UNIVERSITY OF CAPE TOWN : MMED (OBSTETRICS & GYNAECOLOGY)

SUPERVISOR	Dr Nomonde Mbatani
CO-SUPERVISOR	Dr Nazia Fakie
CANDIDATE	Dr Suveshni Govindasamy
STUDY TITLE	A retrospective audit of young patients diagnosed with cervical cancer over ten years at Groote Schuur Hospital, Cape Town between 1 January 2003 and 31 December 2012, and their outcome at five-year follow-up compared to women in the prior decade
DEPARTMENT	Gynaecological Oncology
CONTACT	072 139 7963 suveshnigovindasamy@gmail.com
PROPOSED TIME	1 year
DRAFT NO	CORRECTED AFTER MARKING
SUBMISSION DATE	June 2020

Contents

Declaration – Plagiarism

I, Suveshni Govindasamy, declare that

1. The research reported in this thesis, except where otherwise indicated, is my original research.

2. This thesis has not been submitted for any degree or examination at any other university.

3. This thesis does not contain other persons' data, pictures, graphs or additional information unless specifically acknowledged as being sourced from other persons.

4. This thesis does not include other persons' writing unless recognised explicitly as being sourced from other researchers. These written sources are indicated as follows:

a) Their words have been re-written, with referencing of general information

b) All exact words used have been written in italics, within quotation marks and referenced.

5. This thesis does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source detailed in the thesis and the References sections.

Signed

Student

Signed by candidate

……

Dr Suveshni Govindasamy

STUDY TITLE

A retrospective audit of young patients diagnosed with cervical cancer over ten years at Groote Schuur Hospital, Cape Town between 1 January 2003 and 31 December 2012, and their outcome at five-year follow-up compared to women in the prior decade.

Authors/Supervisor/Co-Supervisor

Govindasamy, S : *MBChB (Stell), Dip Obs (SA), FCOG (SA)*

Mbatani, N : *MBChB (MedUnSA), Dip Obs (SA), FCOG (SA)*

Fakie, N : *MBChB (UCT), FCRadOnc (SA), MMEDRadOnc (UCT)*

ABSTRACT

Background : *Cervical cancer is the second commonest gynaecological cancer amongst women worldwide and the leading cause of cancer deaths in developing countries – contributing 83% of new cases and 85% of all deaths annually to the burden of this disease. Information and awareness of this illness in the developing world is still inferior, and mortality is increasing. In the developing world, late presentation, advanced-stage disease and a poorly run screening programme (covering only 55% of the South African population) are all contributing factors to this statistic. Approximately 20% of all South African women in their reproductive age are also HIV positive. With the rising burden of cervical cancer and the emergence of HIV as an influencing comorbidity, South Africa adopted a national cervical screening programme, rolled out in 2000 as well as an HCT (HIV counselling and testing) programme formalised in 2011. With these initiatives now in place, this study examined trends and compared 5-year survival outcomes between two decades for cervical cancer among young women.*

Methods : *The study undertook a retrospective audit of files and information on the pre-existing cervical cancer database, and appropriate data was extracted (HREC REF 344/2011). Survival and disease outcomes at five years, as well as time to recurrence, was assessed, together with other demographics of the study population. Patients included in the study were non-pregnant female patients, aged 40 years and younger at the time of registration with the Groote Schuur Hospital (GSH) Oncology Unit (LE 33). The diagnosis of cervical cancer had to have been confirmed histologically, as either squamous cell carcinoma or adenosquamous carcinoma or adenocarcinoma. Patients must have attended at the LE 33 unit on or from 1 January 1993 until and including 31 December 2012. The two decades were studied and 5-year outcomes from each decade were analysed and reviewed using Kaplan-Meier curves and univariate analyses. The study compared data using Log Rank tests and p-values.*

Findings : *The two decade-groups under study showed no difference in trends of survival regarding age, treatment type and histology. Albeit small numbers, adenocarcinoma was the histology that had the best probability of survival during both decades. There were more patients with early-stage cancer (stage 1 and 2) diagnosed in decade B (2003 – 2012) than A (1993 – 2002). Within this early-stage cervical cancer cohort, there is a trend toward more locally-advanced (stage 2) cancer in the more recent decade. The proportion of patients presenting with stage 1a and 1b cancer with tumours 4 cm and less has halved from decade A to decade B. The proportion of stage 2 cancers presenting with tumours 2 – 4cm in size during decade B has risen almost 3-fold to that of decade A. This suggests a developing trend of presentation of more locally-advanced cancer. During both decades, stage 1 cervical cancers had the best probability of survival, with an improvement in mean survival from decade A (average of 44 months) to decade B (average of 58 months). The trend of stage 2 disease has deteriorated, with a decrease in mean survival (from 48 months in decade A to 21 months in decade B), an increase in cancer-related deaths and a shorter time to relapse. The number of patients presenting with late-stage disease (stages 3 and 4) has declined. HIV positive status played an influential role in tumour size on presentation and probability of 5-year disease-free survival. Young women who were HIV positive also fared less favourably when compared to NP (not positive) women in terms of mean survival. Due to the small sample size and that the majority of patients in decade A were untested, further HIV comparisons were not credible.*

Interpretation : *The study suggests a moving trend towards young patients that are being diagnosed with the more locally-advanced early-stage disease in the more recent decade than ten years prior. HIV status seemingly played an influential comorbid role in patients diagnosed with cervical cancer. Patients with the locally-advanced disease appear to have worse outcomes in the latter decade. In an attempt to curb this potentially curable disease in this subset of young women, a greater focus on earlier screening interventions, prompt diagnosis and appropriate and timeous treatment of cervical cancer, together with optimisation of comorbidities like HIV are needed.*

Introduction

It is long since known that the human papilloma virus (HPV) is central to the development of cervical neoplasia and can be detected in up to 99,7% of cervical cancer cases.[1] Many high-risk HPV genotypes have been identified: subtypes "*16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82"* have all been linked to cervical cancer with varying virulence.[2] HPV type 16 and 18 on their own are responsible for 70% of all cervical cancers and 50% of cervical cancer precursors worldwide and hence are the main pathogens.[3] Worldwide, HPV infection is known to be the most common sexually transmitted infection (STI). Four out of every five sexually active women will have the virus at some point in their lives.[1] Most women will be asymptomatic and will undergo natural elimination of HPV infection because of a healthy and intact immune system. Persistent infection with a high-risk HPV type puts women at risk to develop precursors of cervical cancer or overt cancer itself. In South Africa, as part of public health response to this severe problem, the HPV vaccine (Cervarix®) was rolled out in April 2014 to school-going girls, aged nine and older, at all public schools. The use of such vaccines still raises many unanswered questions in many respects.[4]

HPV, transmitted easily through sexual intercourse, enters the basal layer of the cervical epithelium at sites of trauma. Once infected with HPV, the cervix reacts by undergoing mild cytological changes and abnormalities. The persistence of high-risk HPV over time results in transformations leading to cervical cancer. Once HPV integrates into the host genome, cytological screening can pick up these changes. Histologically, the genetic aberration is called cervical intraepithelial neoplasia (CIN) and can eventually progress to overt cervical carcinoma, if left untreated. The most common histological subtypes are squamous cell carcinoma (comprising 69% of total cervical cancers) and adenocarcinoma including adenosquamous carcinoma (25% of all cervical cancers).[5,6]

As per the latest GLOBOCAN (Global Cancer Observatory) statistics in September 2018, the data estimated that the cancer burden had increased to 18,1 million cases and 9,6 million deaths, globally. These GLOBOCAN data estimates released in 2018 is based on an online database containing estimates of incidence and mortality in 185 countries for 36 cancer types. [7] As it stands, cervical cancer is the second commonest gynaecological cancer amongst women worldwide and the "*leading cause of cancer-related deaths in developing countries*".[8] In these countries, 83% of new cases and 85% of all deaths contribute annually to the burden of this disease. In Sub-Saharan Africa (SSA), cervical cancer is rated as the most common cancer among women. Information and awareness of this illness in these areas are still inferior, and mortality seems to be on the incline.[9] Delayed presentation, advanced stage of the disease and a poorly functioning screening process are all contributing factors to this statistic.[1]

In an attempt to curb these demographics, in 2000 the South African National Department of Health (DoH) introduced a policy in which every South African woman is entitled to three pap smear tests in her lifetime, done every ten years, starting at the age of 30 (DoH, 2000). This move shows recognition of the severity of the rate of cervical cancer in the country, and a commitment from the government to help rectify the situation and improve statistics. As part of its Women's Health Programme, the DoH's report puts screening as a vital mediation in the prevention of cervical cancer. In SA, a cervical cancer screening rate of 55% was achieved in the year 2011/2012 (DoH, 2012), in comparison to first-world countries where the current screening rate is 72%.[10] The president of the International Gynaecological Cancer Society stressed that cancer prevention efforts should be an imperative focus for countries, as it is anticipated that by 2025 cancer will be a major cause of mortality across all populations.[11,12]

Table 1 gives a timeline of the legislative and policy changes in South Africa, which has had an influence on reproductive health in the country.

Table 1: Major Legislative and Policy Changes Influencing Reproductive Health in South Africa (*Source: Ten Years of Democracy in South Africa: Documenting Transformation in Reproductive Health Policy and Status*)[13]

		Major legislative and policy changes influencing reproductive health in South Africa
1994	-	Department of Health establishes partnerships to plan, process and review HIV/AIDS policy, focusing on the prevention of new HIV infections and treatment of AIDS-related opportunistic infections
	-	Free public health services for pregnant women and children under six
1995	-	Government ratifies the United Nations Convention on the Elimination of All Forms of Discrimination Against Women (CEDAW)
1996	-	Choice on Termination of Pregnancy Act provides a legal framework for the provision of abortion services
1997	-	Maternal death made a notifiable condition; Standing National Committee for Confidential Enquiries into Maternal Deaths established
	-	Patients' Rights Charter launched, giving patients the knowledge and right to address issues of quality in health care services
1998	-	New Population Policy introduced, delinked from population growth
	-	South African National AIDS Council formed
	-	Domestic Violence Act passed
1999	-	Prevention of Mother-to-Child Transmission (PMTCT) of HIV programmes introduced in the Western Cape province
2000	-	National Guidelines for Cervical Screening Programme launched
2001	-	PMTCT programme introduced in Gauteng province
2002	-	Treatment Action Campaign and Children's Right Centre win a court application ordering the government to implement a comprehensive PMTCT programme to prevent Mother-to-Child HIV transmission and to roll out PMTCT services country-wide
	-	National Contraception Policy Guidelines launched
	-	Government approves the provision of HIV post-exposure prophylaxis to survivors of rape in public sector facilities
2003	-	Government approves plan to provide antiretroviral drugs to people with AIDS through public sector services
2004	-	Sexual assault legislation under review to amend the definition of rape and enforce heavier sentences

From the timeline, it is evident that after 1993 the SA government together with the Centre for Disease Control (CDC) became more involved and active with the prevention and treatment of HIV and AIDS-defining illnesses – inclusive of invasive cervical cancer.[14] In 2000, the national cervical screening programme, commonly referred to as the "30-40-50" screening rule, began being rolled out. In April 2011 the South African government started the HIV Counselling and Testing (HCT) movement, a new national campaign to encourage people to know their HIV status and to access counselling and treatment including cervical screening.

The rate of cervical cancer has declined markedly in settings with active cervical cancer screenings. On its own, the sensitivity of the Pap smear is approximately 54%.[1] The newer screening methods, like HPV-DNA testing, are not yet available in the public sector in South Africa. HPV testing is also not yet implemented consistently in the private sector. In developed countries, women are screened every three years for cervical cancer from the age of 21 years (or at the age of sexual debut) until the age of 65 years. Co-testing with cytology and HPV-testing is encouraged from the age of 30, every five years.[15,16] As per the National Cancer Institute, co-testing is more costly but is also a more sensitive means of testing.[17] HPV testing has the advantage of detecting endocervical cancer in younger women better than simple cytology which might miss this diagnosis. The other cost-effective method for screening is visual inspection of the cervix with acetic acid (VIA). This method has been evaluated in multiple cross-sectional studies for its ability to detect HSIL and it has been shown that its sensitivity is quite close to that of cytology (62–80%), but its specificity is much lower (77–84%) when compared to the Pap smear**.** Adequate training and monitoring of this method of testing is needed to evaluate the quality of the visual test.[18] The current most affordable screening tool available in the public sector is thus the Pap smear – and hence needs to be utilised correctly, optimally and maximally. Since 2000, the National Government made no new recommendations or adjustments to the screening protocols. From the Sub-Saharan African statistics quoted, the incidence of invasive cancer of the cervix remains high, the diagnosis is often late in the majority of cases, and many patients have a poor response to treatment.[19]

Cervical cancer screening recommendations differ from country to country and amongst the different organisations. As a comparison to South African recommendations (summarised in table 2b), table 2a summarises the different cervical cancer screening recommendations in the United States of America amongst the different professional organisations.

Table 2a: Cervical cancer screening recommendations from different professional organisations in the United States of America [45,46,47,48]

ORGANISATION	AGE		RECOMMENDED SCREENING TEST & FREQUENCY	
	INITIATION	DISCONTINUATION	AGE 21 – 29 YRS	AGE > 30 YRS
ACS (American Cancer Society) / ASCCP (American Society for Colposcopy and Cervical Pathology) / ASCP (American Society for Clinical Pathology) [2012]	21¶	65Δ	Pap test every 3 years (preferred)	One of these methods: ▪ Co-testing (Pap test and HPV testing) every 5 years (preferred) ▪ Pap test every 3 years
ASCCP (American Society for Colposcopy and Cervical Pathology) / SGO (Society of Gynecologic Oncology) [2015 interim guidelines]	21	N/A	Can consider primary HPV testing every 3 years for women age ≥25	Can consider primary HPV testing every 3 years
USPSTF (United States Preventive Services Task Force) [2018]	21	65§	Pap test every 3 years	One of these methods: ▪ Pap test every 3 years ▪ hrHPV testing alone every 5 years ▪ Co-testing (Pap test and HPV testing) every 5 years
ACOG (American College of Obstetricians and Gynecologist) [2016]	21	65‡	One of these methods: ▪ Pap test every 3 years ▪ Can consider primary HPV testing every 3 years for women age ≥25	One of these methods: ▪ Co-testing (Pap test and HPV testing) every 5 years (preferred) ▪ Pap test every 3 years ▪ Can consider primary HPV testing every 3 years for women age ≥25
ACP (American College of Physicians) [2015]	21	65§	Pap test every 3 years	One of these methods: ▪ Pap test every 3 years ▪ Alternative: Co-testing (Pap test and HPV testing) every 5 years

¶ Regardless of the age of sexual initiation or other risk factors

Δ For women with evidence of adequate negative prior screening (3 consecutive negative cytology results or 2 consecutive negative co-tests within the previous 10 years, with the most recent test within the previous 5 years) and no history of CIN 2 or greater within the last 20 years. Screening should not be resumed for any reason, even if a woman has a new sexual partner

§ For women with evidence of adequate negative prior screening, specified as 3 consecutive negative cytology results or 2 consecutive negative co-tests within the previous 10 years, with the most recent test within the previous 5 years

‡ For women with no history of CIN 2 or higher with evidence of prior adequate screening (3 or more negative cytology test results in a row or 2 consecutive negative co-tests in the past 10 years, with the most recent within the past 5 years)

In South Africa, the South African Society of Obstetricians and Gynaecologists (SASOG) released a recent guideline on cervical screening in South Africa in 2015. This was developed by a team of professional experts from public health, virology, gynaecological oncology, anatomical pathology and cytology. It is the third guideline to be reviewed and published. It advises that in a low or high resource South African setting, screening should commence at the age of 25 years if the woman is HIV negative, otherwise, at the time of diagnosis if HIV positive. Screening should terminate at hysterectomy, provided that the tests were negative or at the age of 65 in high resource settings and the age of 55 years in the low resource setting. For those who are HIV positive, screening should never stop.[20] Table 2b summarises these recommendations:

Table 2b: Primary Screening Guidelines as per SASOG [20]

	LOW RESOURCE SETTING	HIGH RESOURCE SETTING
Initiate Screening	Age 25 At diagnosis of HIV positivity	Age 25 At diagnosis of HIV positivity
End Screening	Age 55 or hysterectomy (After previous negative tests)	Age 65 or hysterectomy (After previous negative tests)
Never End Screening	HIV positive	HIV positive
Interval HPV Test	10 years if HIV negative or unknown 5 years if HIV positive	5 years if HIV negative or unknown 3 years if HIV positive
Interval Cytology	5 years if HIV negative or unknown 3 years if HIV positive	3 years if HIV negative or unknown Yearly if HIV positive
Timing	Ten-yearly: At ages 25, 35, 45, 55 Five-yearly: Also at ages 30, 40, 50 Three-yearly: At ages 25, 28, 30, 33, 36, 40, 43, 46, etc	Five-yearly: Also at ages 30, 40, 50 Three-yearly: At ages 25, 28, 30, 33, 36, 40, 43, 46, etc Yearly: each year
Follow-up	After single abnormal screening test or after treatment: - HIV negative and <35years: 5 yearly until normal - HIV positive or >35years: yearly until normal Back to SCREEN when normal Treat after second abnormal test	After single abnormal screening test or after treatment: - HIV negative and <35years: yearly until normal - HIV positive or >35years: yearly until normal Back to SCREEN when normal Treat after second abnormal test

From Table 2b, it is evident that an attempt to increase surveillance in the HIV positive population is underway since South Africa has one of the highest incidences of HIV, affecting 13,1% of the population, as per the 2018 report by Stats SA (Statistics South Africa). Approximately one-fifth of women in their reproductive age (15–49 years) are HIV positive.[21] Unlike other AIDS-defining neoplasms such as Kaposi's sarcoma and non-Hodgkin's lymphoma, the development of cervical cancer is not solely dependent on immune compromise. HIV alters the natural history of HPV infection by causing a faster development to high grade and invasive lesions that are resistant to treatment, or which regress at a much slower rate. The more aggressive course is due to an interaction between

HPV and HIV viral proteins. HIV enhances the effectiveness of HPV proteins, resulting in a change in the molecular pathway and perhaps, to cell cycle disruption.[22]

The detection of HPV infection increases quite rapidly within the first years after HIV seroconversion. This raises the hypothesis that mucosal immune dysfunction occurring at an early stage of HIV infection might influence HPV-related diseases. Wang et al. showed that among HIV seroconverters, HPV infection prevalence doubled at and after seroconversion, compared to before seroconverting. HIV seroconversion was associated with newly detected HPV infection and increased risk of low-grade cytological abnormalities.[23]

In Africa, over the past few years, the incidence of cervical cancer has increased among younger women, driving the WHO to warn low-resource areas that global cervical cancer deaths will increase to 460 000 by the year 2040 – and that low- and middle-income countries (LMICs) will have the greatest relative increase.[24] Furthermore, it has been noted that younger patients with cervical cancer have worse clinical and overall survival outcomes.[25,26] Patient age also seems to be an independent determining factor for early recurrence of cervical cancer.[27] Characteristics like poor tumour differentiation and lymph node metastasis in these younger patients may collectively contribute to early recurrence of cervical cancer in this patient population subset.[28]

Approximately 7 out of 10 women will remain alive five years after diagnosis, in first world countries compared to many developing countries, who have an overall survival rate of less than 40%.[29]

One of the essential factors in determining the treatment and prognosis of cervical cancer is the staging of the disease. Other factors include the age of the patient, the HIV status, parametrial involvement, tumour histology and general health of the patient.[30] Table 3 provides a summary of the overall five-year survival rates according to the stage of the disease, by FIGO (International Federation of Gynaecology and Obstetrics).[31]

Table 3 : Percentage of women alive after five years, inclusive of all age groups : 1999 to 2001 (as per FIGO statistics)

STAGE	% OF WOMEN ALIVE AFTER 5 YEARS
IA1	97,5%
IA2	94,8%
IB1	89,1%
IB2	75,7%
IIA	73,4%
IIB	65,8%
IIIA	39,7%
IIIB	41,5%
IVA	22,0%
IVB	9,3%

This study gathered recent institutional statistics to gain better insight into the institution's performance and trends over the decades.

Methods

Single institution study

The research and data collection for the study took place at the Groote Schuur Hospital Gynaecological Oncology Unit (LE33), in Cape Town, Western Cape, South Africa.

Time

The study analysis was from 1 January 2003 until 31 December 2012 and compared to the previous decade (1 January 1993 until 31 December 2002).

Study design

The study conducted a retrospective audit of files from 1 January 1993 until 31 December 2012 and appropriate data extracted. Survival and disease-free outcomes at five years, as well as time to recurrence, was assessed, together with other demographics as dictated by the study outcomes.

Study population

The inclusion criteria were non-pregnant female patients, aged 40 years and younger at the time of registration with the Groote Schuur Hospital (GSH) Oncology Unit (LE 33). These patients had to have a histologically confirmed cervical cancer. Only squamous cell carcinoma, adenosquamous carcinoma and adenocarcinoma histology were included. Patients must have attended at the LE 33 unit on or from 1 January 1993 until and including 31 December 2012.

Patients excluded from the study were those women who were pregnant upon entry into the unit, those aged 41 years and older and those patients diagnosed with histology other than squamous, adenosquamous and adenocarcinoma. Patients receiving treatment at any other oncology unit in the Western Cape or South Africa were excluded from this study.

Study aim

This study aimed to compare trends in the 5-year survival outcomes for cervical cancer (adenocarcinoma, adenosquamous carcinoma and squamous cell carcinoma) in women 40 years and younger, using data from the Gynaecological Oncology Unit (LE33) at Groote Schuur Hospital from 1 January 2003 until 31 December 2012, and to compare this data to the preceding decade.

Study outcomes

This study analysed three primary outcomes: five-year overall survival, five-year disease outcome and the time to recurrence.

The secondary outcomes in this retrospective audit assessed the clinical and pathological characteristics of patients diagnosed with cervical cancer at 40 years or younger. It also evaluated the influence that HIV status has on cervical cancer. Clinical features that were analysed were age at entry into the unit (age at diagnosis), stage at diagnosis, HIV status, haemoglobin (Hb) level at presentation, tumour size clinically, presence of hydronephrosis, parametrial involvement and treatments offered.

The above outcomes studied for each of the ten years (1 January 1993 – 31 December 2002 and 1 January 2003 – 31 December 2012), were compared and analysed.

Study method

The database used for the collection was Microsoft Excel 2016. An electronic data capturing device (Samsung Tab A 10,1) aided in capturing data electronically. The author's laptop (Acer Aspire V) then received this data. All data was backed-up to an external hard-drive. The author printed a hard-copy of the captured data, carefully filed, analysed and stored it in a locked cupboard.

The author ensured the security and confidentiality of the data at all times in the following ways:

- The anonymity of patients included in the study was maintained by identifying patients by a specially allocated number, rather than by name or folder number during the data collection and capturing on the datasheet
- Documents are all password protected
- All changes to the data capturing document saved as new versions and all devices had up-to-date virus protection.
- No data was sent via or uploaded to the internet.
- Secure and private electronic versions of write-ups (including the concept note, the research proposal, the university forms for submission and the write up of the article post data analysis) were used and sent via email to communicate to supervisors, due to interprovincial distance between supervisors and student

Files containing patients' one-page summaries ('registration forms') completed by the multidisciplinary team at the Combined Assessment Clinic (CAC) at GSH LE 33 unit, during the period 1 January 1993 until 31 December 2012, and who met the inclusion criteria of the study, were collected and analysed for data pertaining to the aims of this study. The data extracted from these folders assisted with comparison and supplementation to the information on the existing database at LE33 Gynae Oncology. Data was then analysed to obtain relevant information to meet the primary and secondary study outcomes.

Ethical clearance and consent

The database approval number is HREC REF 344/2011. The University of Cape Town (UCT) HREC granted ethical approval for this study – HREC REF 143/2020.

The Chief Executive Officer (CEO) of GSH granted institutional consent (Appendix 1). Permission to conduct my study at the gynaecological oncology unit LE33 and to allow me to use to the relevant records was granted by the unit's Head of Department (HOD) (Appendix 2).

Budget

The budget, inclusive of travel expenses, data and internet, stationery, printing, postage and biostatistical analysis, was all self-funded.

Clarity and study definitions

A glossary of the abbreviations used in this article appears at the end of the article, listed alphabetically. For clarity and universality, it is important to note the following in the context of this study:

- The staging of cervical cancer adopted in this study is the clinical FIGO Staging revised in 2009.
- The guidelines and protocols practised at Groote Schuur Hospital, are per the National Cancer Institute (NCI) guidelines.
- 'Early-stage cancer' or 'early cervical disease' refers to stage 1 and 2 cervical cancer, and stage 3 and 4, will be termed 'late-stage cancer/disease' for the scope and comparison in this study.
- For ease of comparison, the period 1 January 1993 through to 31 December 2002, will be referred to as 'decade A' and the following ten years (1 January 2003 through to 31 December 2012), will be referred to as 'decade B', to avoid any confusion.

- The term ‘young women’ refers to those patients 40 years and younger, while those women referred to as being in the ‘older’ age group incorporates those patients 41 years and older.
- Women grouped and termed as ‘NP’ (not positive), are those patients who were tested and found to be HIV negative as well as those patients who were never tested or never had their test result recorded (‘not specified’).

Analysis

After collecting, supplementing and cross-checking the data, the data was then anonymised and cleaned - keeping the primary and secondary outcomes in mind. An actuary then analysed the data. Crude Kaplan-Meier curves were drawn for the primary outcomes and tested for statistical significance using Log Rank tests. Secondary outcomes were analysed through univariate analyses and tested for statistical significance using p-values.

Tables and graphs show the results and observations to better understand and view comparisons between the two decades under study.

Results

Flow of patients in the study

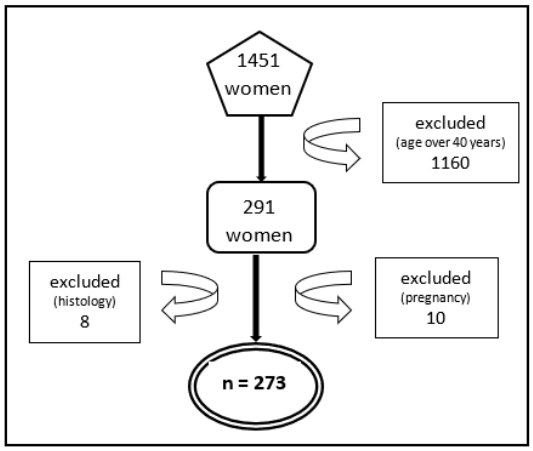
As per Figure 1, in decade A, there were a total of 1451 patients that were in the cervical cancer database, of which 1160 patients (80%) did not fulfil the age criteria. This left 291 patients (20%) that were 40 years and younger during this decade. Excluded patients comprised ten pregnant women (3%) and a further eight (3%), based on the histology exclusion criteria. The median age at diagnosis, in those 40 years and younger during decade A was 36 years.

There were a total of 1695 women that entered the unit diagnosed with cervical cancer during decade B. In this decade, 1350 patients (80%) were 41 years and older. After applying the inclusion criteria, 310 women (18%) were left for analysis in this decade, with a median age of 35 years.

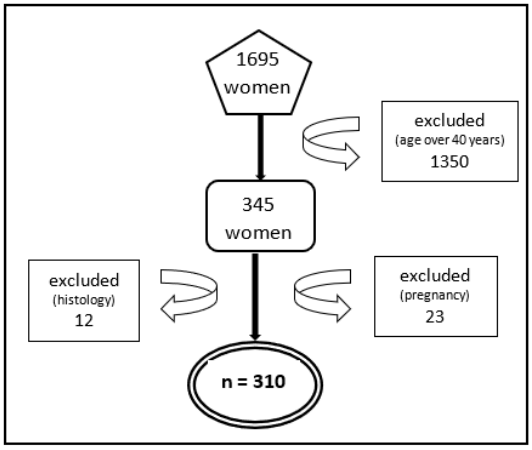
The two groups were comparable in age and size.

Figure 1 : Flow of patients in the study

Decade A



Decade B



For ease of comparison and to obtain better clarity of the population subset under study, the author decided to report on the secondary outcome results first and then those of the primary outcomes.

SECONDARY OUTCOMES

Age at entry into the unit

Age at entry into the unit was taken as a measure of 'age at diagnosis' when the patient entered the LE 33 unit at GSH, for this study. Trends were analysed to see the distribution of patients.

Table 4a, Table 4b and Figure 2 show the spread of the patients included in the study for each decade, according to the age distribution, HIV status, histology and stage of cancer at diagnosis.

Young women (those 40 years and younger), accounted for approximately 20% of all the patients on the database for each decade. Of this, 49 patients (18%) and 51 patients (16%) were under the age of 30 years in decade A and B, respectively. The highest incidence, in each decade, was in patients between age 31 to 40 years. This group will likely not benefit from the South African cervical cancer screening guidelines implemented. There is no difference in the trend of age between the decades. (p=0,63).

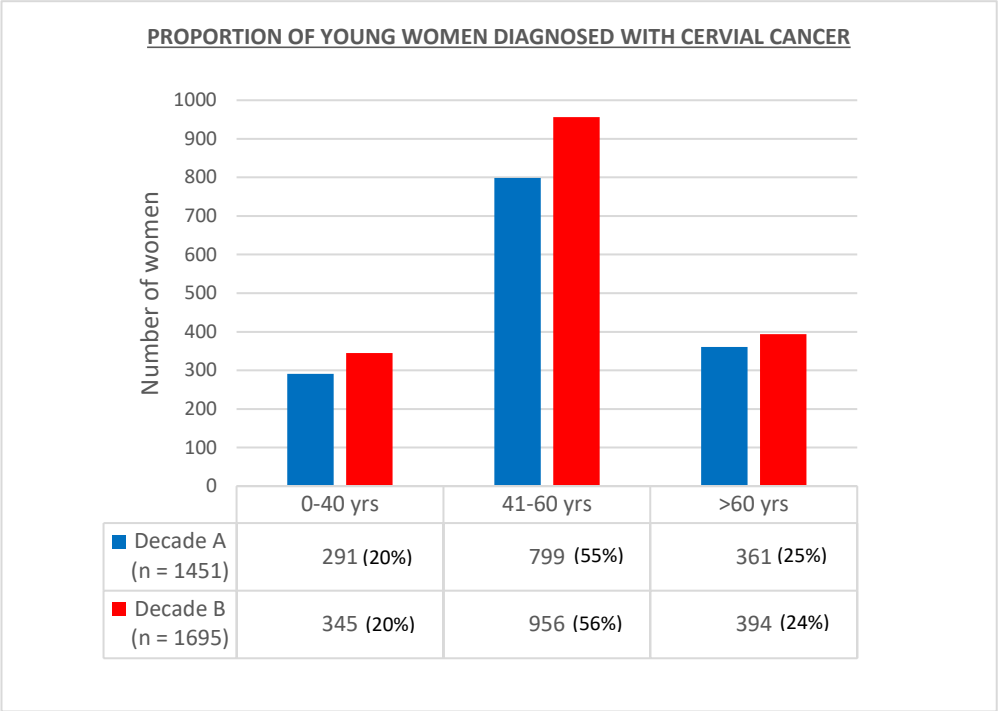
Table 4a : Distribution of patients by age group, according to HIV status, histology and stage of cancer during Decade A

		Decade A (n = 273)									
Age	**N**	**HIV Status**			**Cervical Cancer Histology**			**Stage of Cancer**			
		POS	***NEG***	***NS***	***Adenocarcinoma***	***Squamous***	***Adenosquamous***	***ia***	***ib***	***ii***	***iii&iv***
0-20	0	0	0	0	0	0	0	0	0	0	0
21-30	49	5	6	38	2	46	1	4	11	7	27
31-40	224	7	32	185	20	185	19	24	65	46	89
Total	**273**	**12**	**38**	**223**	**22**	**231**	**20**	**28**	**76**	**53**	**116**
% of total		**4%**	**14%**	**82%**	**8%**	**85%**	**7%**	**10%**	**28%**	**19%**	**42%**

Table 4b : Distribution of patients by age group, according to HIV status, histology and stage of cancer during Decade B

		Decade B (n = 310)									
Age	**N**	**HIV Status**			**Cervical Cancer Histology**			**Stage of Cancer**			
		POS	***NEG***	***NS***	***Adenocarcinoma***	***Squamous***	***Adenosquamous***	***ia***	***ib***	***ii***	***iii&iv***
0-20	0	0	0	0	0	0	0	0	0	0	0
21-30	51	23	28	0	3	46	2	11	10	28	2
31-40	259	79	156	24	17	235	7	31	51	162	15
Total	**310**	**102**	**184**	**24**	**20**	**281**	**9**	**42**	**61**	**190**	**17**
% of total		**33%**	**59%**	**8%**	**6%**	**91%**	**3%**	**14%**	**20%**	**61%**	**5%**

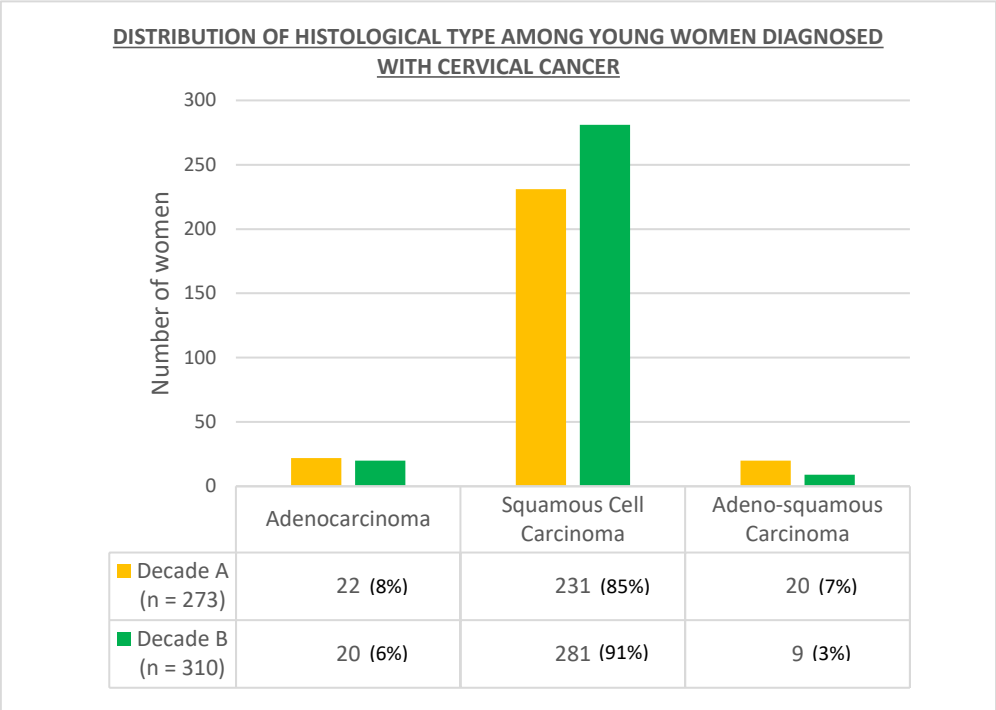
Figure 2 : Distribution of young women diagnosed with cervical cancer according to age



Histology

The histological distribution of cervical cancer during each decade (Figure 3) has remained similar: 85% of patients (231) during decade A diagnosed with squamous cell carcinoma while 90% of patients (281) during decade B had the same histological type. Adenocarcinoma was present in 8% (22 patients) of those young women in decade A and 6% (20 patients) of those in decade B. The incidence of adenosquamous histology has decreased only slightly from 7% (20 patients) in decade A to 3% (9 patients) in the more recent decade B. No change in the trend of histological distribution occurred over the two decades (p=0,99 for each histological type).

Figure 3 : Distribution of histological type among young women diagnosed with cervical cancer



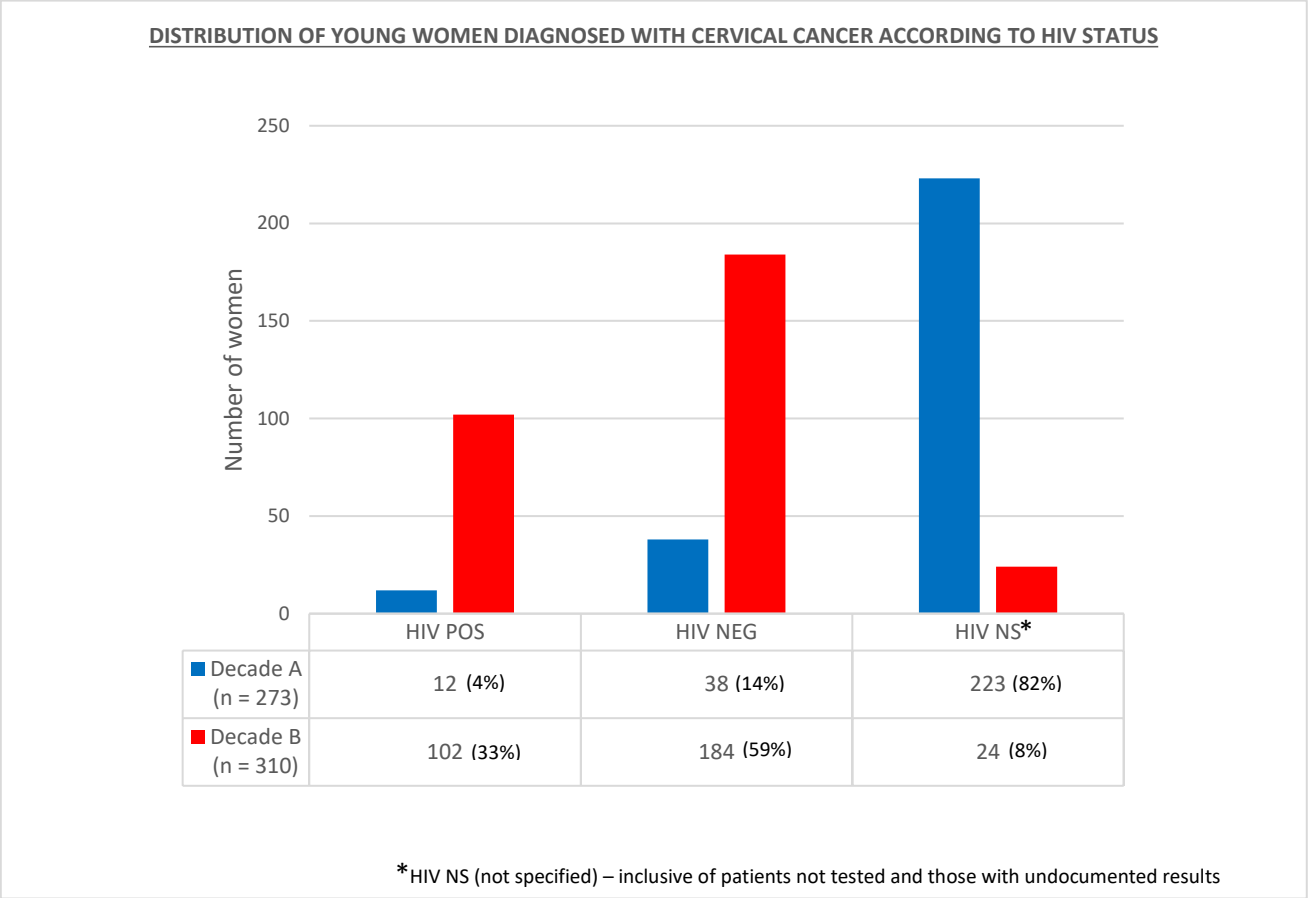
HIV Status

There was no routine documentation done of patient's HIV status on the cervical cancer database or the LE 33 Combined Assessment Clinic registration form, especially for the first ten years under study. Attempts at obtaining this information physically or electronically via the NHLS (National Health Laboratory Service), the NHLS TrakCare website or the DISA Website proved unsuccessful due to the period under study going back as far as it did. Figure 4 clearly shows that during decade A, the recording of patients' HIV status was sparse and hence, more than 80 % of patients in this decade fell in the 'not specified' group. Only 4% of patients (12) were documented as being HIV positive, while 14% (38 patients) were negative. Although HIV counselling and testing began formally in 2011 on the government roll-out initiative, Groote Schuur Hospital did start a rigorous recording of patient's HIV status before then – notable in the second ten-year period under study. This shift in awareness and testing resulted in the marked improvement seen in Figure 4 during decade B, where 92% (286) of patients had their HIV status documented and recorded. In this decade, a third of patients (102) were HIV positive, and 59% (184 patients) documented as HIV negative.

Further analysis with regards to whether HIV positive patients were on ARV (antiretroviral) treatment, which regimen they were on, their viral load or if they were ARV-naïve or newly

diagnosed at the time of cervical cancer diagnosis were not reviewed or assessed during this study.

Figure 4 : Distribution of young women diagnosed with cervical cancer according to HIV status

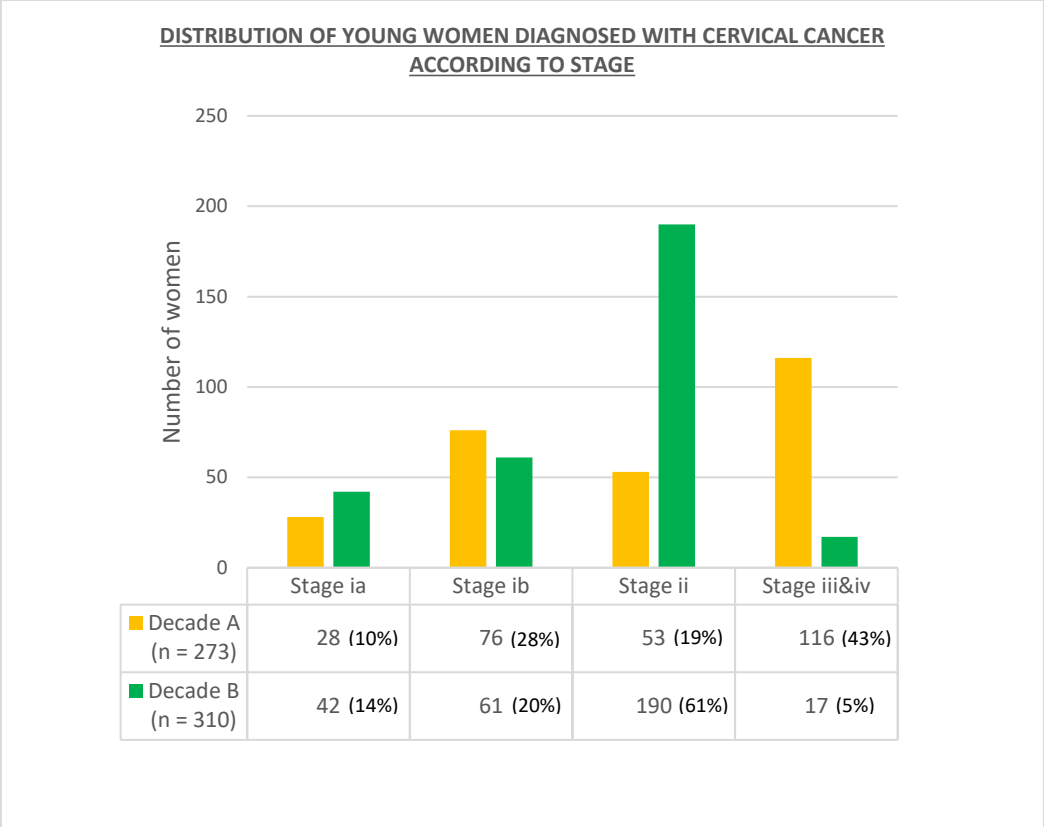


The stage at entry into the unit

This was taken as a measure of 'stage at diagnosis'. Figure 5 indicates that each of the decades differs with regards to stage at diagnosis. During decade A, 157 patients (58%) presented with early-stage disease – comprising of 66% (104) of stage 1 patients and 34% (53) of stage 2 patients. In decade A, 116 patients (42%) presented with late-stage cancer. Decade B's trend shows that 293 patients (95%) presented with early-stage cancer – 33% (103) stage 1 and 62% (190) stage 2; while only 17 (5%) patients had late-stage disease. This could be an indication that a fair amount of younger women report abnormal vaginal bleeding and discharge, associated with cervical cancer while some had their diagnosis made during screening.

The proportion of all early-stage cancers in decade A was not significantly similar to that in decade B (p<0,0001). Out of the early-stage cervical cancer cohort, stage 2 proportion is not significantly static between the two decades (p<0,0001). Hence, there were more patients diagnosed with stage 2 cervical cancer in decade B than in A. The reason for this finding could be that patients may have presented with probably, bigger tumours with parametrial involvement. It was difficult to correlate this with HIV status, as HIV testing and documentation in patients with cervical cancer was not routine during the prior decade.

Figure 5 : Distribution of young women diagnosed with cervical cancer according to stage



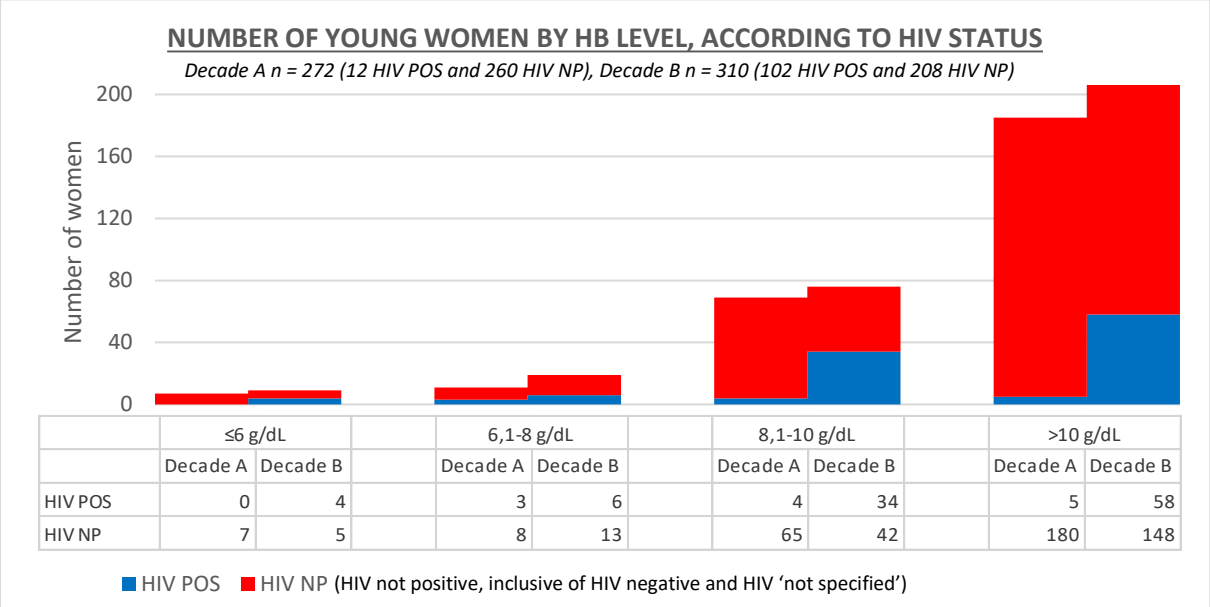
Initial Haemoglobin (Hb) at presentation

The patient's Hb at presentation to LE 33 unit, together with its trends, were analysed. This study did not analyse further information about whether patients had received a blood transfusion or intravenous or oral iron supplementation before being seen at the unit. Only one patient during decade A had no initial Hb level documented.

Figure 6 shows that during both decades, the majority of patients have fairly good Hb's (8g/dL and above) at entry into the LE 33 unit, independent of HIV status. Low Hb level at presentation could be related to the severity of the bleed and the chronic nature of cancer.

The Hb level at initial presentation has shown not to have deteriorated with the passing decades, despite the rising HIV awareness and statistics. Information on the administration of blood or iron transfusion or supplementation before the initial LE 33 unit presentation would have been helpful to obtain a better clinical picture of this parameter and its effect on treatment and survival outcomes.

Figure 6 : Distribution of young women diagnosed with cervical cancer by Hb level, according to HIV status



	≤6 g/dL		6,1-8 g/dL		8,1-10 g/dL		>10 g/dL	
	Decade A	Decade B	Decade A	Decade B	Decade A	Decade B	Decade A	Decade B
HIV POS	0	4	3	6	4	34	5	58
HIV NP	7	5	8	13	65	42	180	148

Cancer stage: tumour size, hydronephrosis and parametrial involvement

Information regarding tumour size, hydronephrosis and parametrial invasion were collected and analysed to gain further insight into cancer 'aggression'.

Tumour size in almost all patients with cervical cancer was measured clinically. Therefore, measurements are mainly subjective. Table 5 reviews tumour size according to early-stage cancer for each decade. Of all the early-stage cancers (stage 1a, 1b and 2) during decade A, 104 patients (66%) with stage 1 (1a and 1b) cancers, had presented with tumours 4cm and less in size. This was the case for only 99 patients (34%) of the same subset in decade B. The proportion of stage 1 cancers with tumours 4cm and less is significantly different between the decades (p<0,0001). The proportion of women with tumours 0 – 2cm in size in decade A is significantly less than the equivalent group in decade B (p<0,001). For tumours 2 – 4cm in size, there was a larger proportion of patients during decade B than during decade A (p<0,001). Approximately 5% of patients (8) in decade A with tumours more than 4cm had stage 2 cervical cancer and 10% (24) of stage 2 cancer patients in decade B had tumours more than 4cm; however, this increasing trend is not statistically significant (p=0,22).

Figure 7 graphically depicts that the majority of patients, whether HIV positive or not, present with an average tumour size of 2 to 4 cm on clinical examination, in both decades A and B. Due to the small number of HIV patients during decade A, reliable comparisons could not be made. During decade B, for tumours 0 – 4 cm in size, HIV status is shown not to be significantly independent of tumour size (p=0,02). The sample cohort for tumour size larger than 4 cm in decade B was too small to analyse further.

Table 5 : Distribution of the number of young women according to tumour size, by cervical cancer stage

Tumour Size	Decade A (n = 157)			Decade B (n = 293)		
	Stage of Cancer			Stage of Cancer		
	ia	*ib*	*ii*	*Ia*	*ib*	*Ii*
0-2 cm	28	54	7	42	44	5
2,1-4 cm	0	22	38	0	13	161
>4 cm	0	0	8	0	4	24
Total	**28**	**76**	**53**	**42**	**61**	**190**
% of total	**18%**	**48%**	**34%**	**14%**	**21%**	**65%**

Figure 7 : Distribution of tumour size in young women diagnosed with cervical cancer, according to HIV status

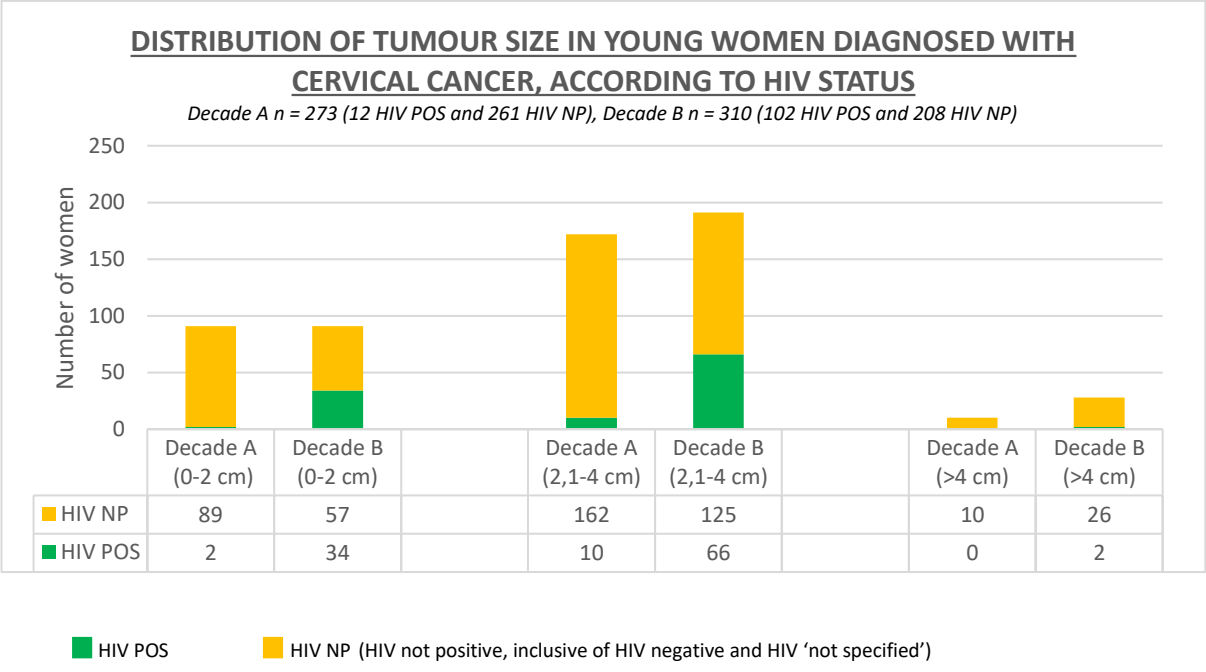


Table 6a shows that the proportion of patients with hydronephrosis and late-stage cancer, during decade A and B, do not differ significantly (p=0,67). From Table 6b, it is evident that patients with late-stage cancer without hydronephrosis have similar trends between the decades: in decade A, a mean survival of 30 months (median 16 months) for stage 3b and 6 months (median 4,5 months) for stage 4, while in decade B the same population subset has a mean survival of 25 months (median 15 months) and 6 months (median 4 months) respectively. A sub-analysis of mean survival in patients with stage 3b disease indicated that the presence of hydronephrosis (whether unilateral or bilateral) had remained unchanged from decade A (mean 13 months) to decade B (mean 12 months). The median survival increased from 4,5 months during decade A to 9 months in decade B. Stage 4 cancer patients with hydronephrosis showed the biggest difference, where their mean survival drops from 8 months (median 4 months) in decade A to 3 months (median 2 months) in decade B; however this finding proved not statistically significant (p=0,1).

Table 6a : Distribution of the number of young women with hydronephrosis, according to late stages of cervical cancer

	Decade A (n = 114)		**Decade B (n = 152)**	
Hydronephrosis	**Stage of Cancer**		**Stage of Cancer**	
	iiib	***iv***	***iiib***	***Iv***
NIL	51	15	76	8
UNI	26	5	33	5
BIL	9	8	26	4
Total	**86**	**28**	**135**	**17**
% of total	**75%**	**25%**	**89%**	**11%**

Table 6b : Mean survival in months of young women with and without hydronephrosis, according to late stages of cervical cancer

	Decade A (n = 114)		Decade B (n = 152)	
Hydronephrosis	**Stage of Cancer**		**Stage of Cancer**	
	iiib	***iv***	***iiib***	***Iv***
ABSENT	30	6	25	6
PRESENT	13	8	12	3

Table 7a shows that during decade A and B, the proportion of patients with unilateral parametrial involvement has significantly decreased (p<0,0001), while those with bilateral (p=0,02) and pelvic sidewall invasion have significantly increased (p=0,04). Table 7b shows that the mean overall survival of patients with parametrial involvement (unilateral and bilateral) as well as those patients with pelvic sidewall invasion have not changed significantly from decade A to decade B (p=0,05).

Table 7a : Distribution of the number of young women with parametrial involvement, according to the late stages of cervical cancer

	Decade A (n = 135)		Decade B (n = 189)	
Involvement	**Stage of Cancer**		**Stage of Cancer**	
	iib	***iii***	***iib***	***Iii***
NIL	0	0	0	1
UNI	33	18	20	15
BIL	15	64	34	101
PSW	0	5	0	18
Total	**48**	**87**	**54**	**135**
% of total	**36%**	**64%**	**29%**	**71%**

Table 7b : Mean survival in months of young women with and without parametrial involvement, according to late stages of cervical cancer

	Decade A (n = 135)		Decade B (n = 189)	
Involvement	**Stage of Cancer**		**Stage of Cancer**	
	iib	***iii***	***iib***	***Iii***
NIL	-	-	-	60
UNI	45	34	43	24
BIL	34	18	31	12
PSW	-	51	-	57

Treatments received

Young women who met the inclusion criteria for the study were analysed and compared according to the treatments they received. The guidelines and protocols practised at Groote Schuur Hospital, are per the National Cancer Institute (NCI) guidelines. Treatment of cervical cancer is stage-dependent and therapies were grouped into six categories, as follows (the corresponding group depicted in Figure 8 shown in parenthesis below):

1. surgery with or without EBRT (external beam radiotherapy), adjuvant vault brachytherapy or adjuvant EBRT and vault brachytherapy (group 1)
2. EBRT followed by brachytherapy (group 2)
3. chemotherapy only (group 3)
4. concurrent chemotherapy (group 4)
5. vault brachytherapy or EBRT alone (group 5)
6. palliative care (group 6)

The data was incomplete for only one patient in decade A. As depicted in Figure 8, during decade A the majority of patients received treatment groups 1 or 2. Concurrent chemo-radiotherapy has shown to improve survival in patients with locally advanced cervical cancer.[32,33] Following the evidence from the literature, the majority of patients in decade B received concurrent chemotherapy (87 patients in treatment group 4) or surgery (91 patients in treatment group 1), followed then by radiotherapy (50 patients in treatment group 2). Only in exceptional cases, surgery after chemotherapy occurred (e.g. young women with cervical cancer diagnosed in pregnancy). The graph in Figure 8 demonstrates this evident shift in management from 1999 onwards where the implementation of a combination of radiotherapy and chemotherapy began to manage patients in decade B, in contrast to decade A where young women with cervical cancer received mainly

radiotherapy without chemotherapy. In decade A, there is a spread of treatments received, but given the small overall HIV positive subset, there are no evident material trends. As expected, in decade B (given that in practice treatment is not HIV-dependent), the data shows no clear relationship between HIV status and treatment type.

Figure 8 : Distribution of different types of treatment received in young women diagnosed with cervical cancer, according to HIV status

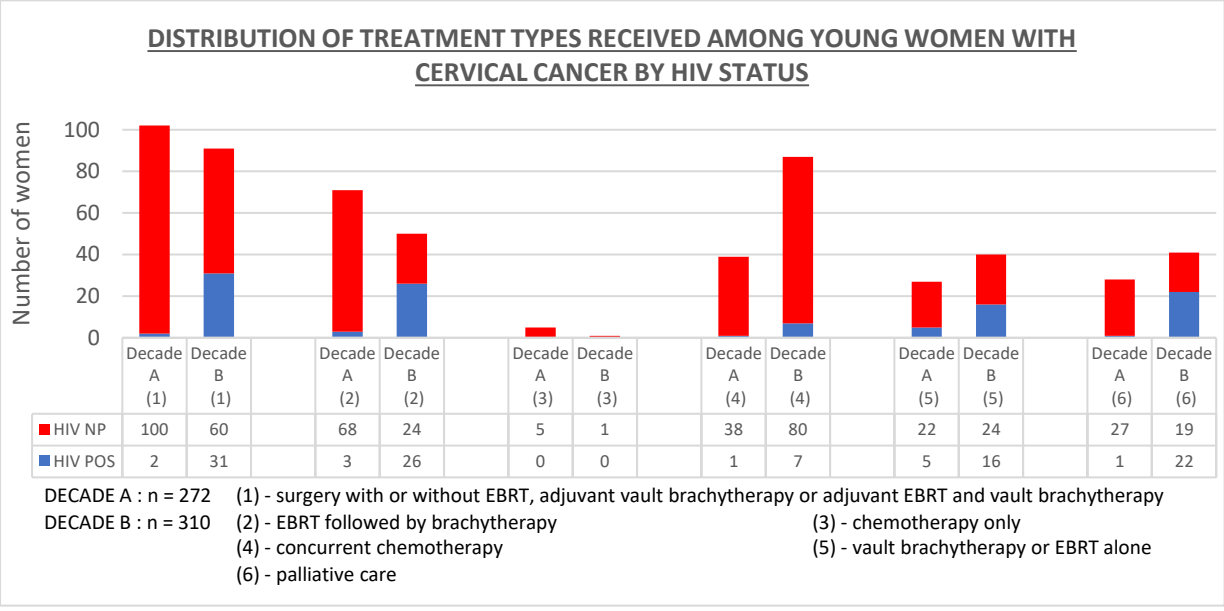
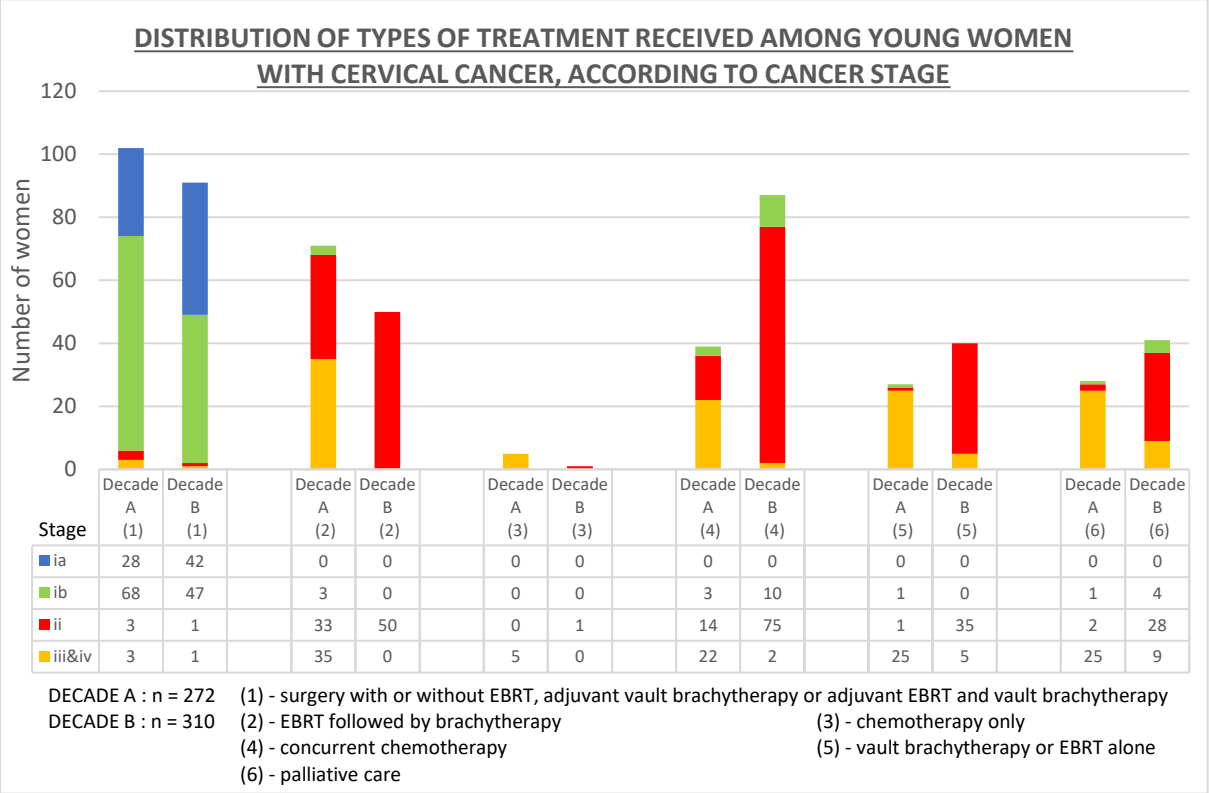


Figure 9 shows that since cervical cancer treatment is stage-dependent, the majority of stage 1 disease in both decades received surgery with or without radiotherapy (treatment group 1). The proportion of stage 2 cancers that received radiotherapy significantly increased from decade A to B ($p<0,001$). A similar significant increase occurred for those patients who received concurrent chemotherapy ($p<0,01$).

Figure 9 : Distribution of different types of treatment received in young women diagnosed with cervical cancer, according to stage



Stage	Decade A (1)	Decade B (1)	Decade A (2)	Decade B (2)	Decade A (3)	Decade B (3)	Decade A (4)	Decade B (4)	Decade A (5)	Decade B (5)	Decade A (6)	Decade B (6)
ia	28	42	0	0	0	0	0	0	0	0	0	0
ib	68	47	3	0	0	0	3	10	1	0	1	4
ii	3	1	33	50	0	1	14	75	1	35	2	28
iii&iv	3	1	35	0	5	0	22	2	25	5	25	9

DECADE A : n = 272
DECADE B : n = 310

(1) - surgery with or without EBRT, adjuvant vault brachytherapy or adjuvant EBRT and vault brachytherapy
(2) - EBRT followed by brachytherapy
(3) - chemotherapy only
(4) - concurrent chemotherapy
(5) - vault brachytherapy or EBRT alone
(6) - palliative care

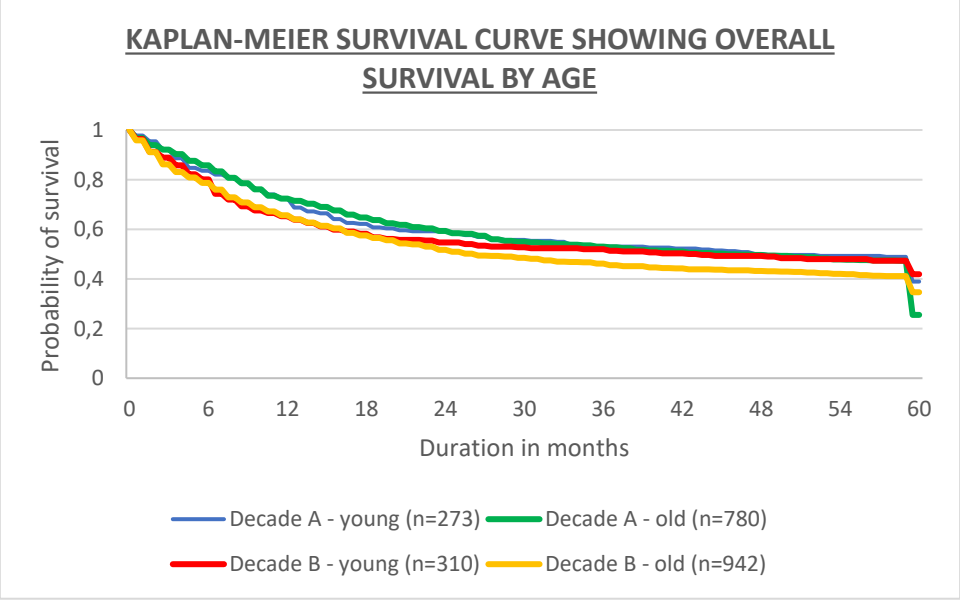
PRIMARY OUTCOMES

5-year overall survival

In this study, six categories of survival curves were drawn up and analysed to compare decade trends.

The first curve analysed was survival according to age groups, comparing young women with cervical cancer (those 40 years and younger) with those women 41 – 60 years of age in decade A and decade B (Figure 10). Figure 10 illustrates that during decade A, the older age group had an overall survival trend very similar to that of the younger age group – no statistical difference was observed (p=0,31). However, in decade B, the younger and older age groups initially follow a similar survival trend until approximately 20 months, where after the younger population shows a better probability of survival than the older age group. However, once again, this observation is not statistically significant (p=0,9). Looking more closely at the subset of patients included for this study (those 0 – 40 years), the overall survival of this younger subset of women during decade A was only marginally better but not statistically significant over earlier durations than that during decade B (p=0,6). Hence, there was no statistically significant difference in overall survival in younger women (0 – 40 years) from decade A to decade B.

Figure 10 : Probability of survival according to age



The second survival curve analysed, evaluated the probability of survival in those patients meeting the inclusion criteria of the study that were HIV positive versus those women who were HIV negative and those unspecified (referred to as 'NP' – not positive), in each decade (Figure 11). Data were analysed and compared to see the trend, even though there were markedly fewer HIV status recordings in decade A.

Figure 11 shows that in both decades A and B, HIV positive patients had a slightly worse overall probability of survival than those diagnosed as HIV NP (p=0,73 for decade A and p=0,88 for decade B). It can also be noted that conditional on 3-year survival, HIV positive patients in decade A (albeit few) had subsequently better 5-year survival outcomes (very similar to those HIV NP patients in both decade A and B) compared to those in decade B, however, this proved not to be statistically significant (p=0,29). Therefore, there is not enough convincing evidence to show a difference in overall survival outcomes based on HIV status.

The actual mean survival in months in those HIV positive and NP women has decreased from decade A to decade B, as depicted in Table 8. Patients with a NP status have better mean survival than those that are status positive during both decades.

Figure 11 : Probability of survival in young women with cervical cancer, according to HIV status

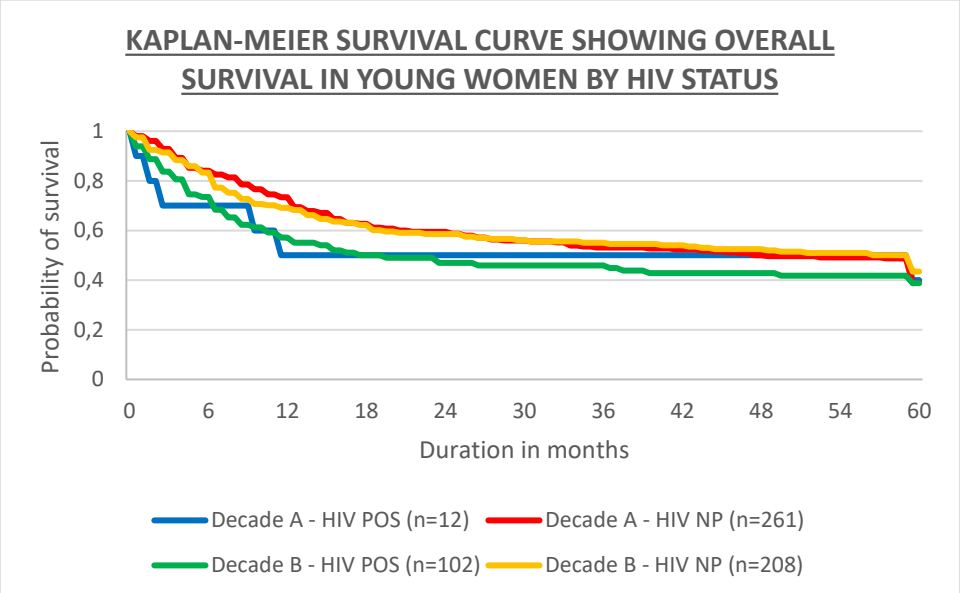


Table 8 : Mean survival in months of young women diagnosed with cervical cancer, according to HIV status

HIV Status	Decade A (n=273)	Decade B (n=310)
HIV POS	35	26
HIV NP	37	29

Figures 12a and 12b show the Kaplan-Meier curves comparing the stage at diagnosis (taken from the stage at entry into the unit) in each decade for those women meeting the inclusion criteria for the study.

Across all durations, cervical cancer stage 1a and 1b have the best probability of survival. Decade B's stage 1b patients appear to show an improvement in survival when compared to the equivalent decade A stage 1b patients' survival; however, this proved not to be statistically significant (p=0,94). No significant difference in overall survival among women with stage 2 cancer during decade A and B was noted (p=0,99). Late-stage cervical cancer (stage 3 and 4), has the worst survival probability for both decade A and B, with no significant difference in change of trend pattern observed from decade A to decade B (p=0,99).

Table 9 shows that there has been an improvement in mean survival time from decade A to decade B in stage 1a and 1b cervical cancer. There is a decrease in the mean survival of approximately 50% from decade A to decade B in those women with stage 2 cervical cancer. Late-stage cancer's mean survival has also decreased from 24 months in decade A to 3 months in decade B. This shows a deterioration in mean survival in patients with stage 2 and late-stage cancer when compared to the prior decade A.

Figure 12a : Probability of survival in young women with cervical cancer, according to stage during decade A

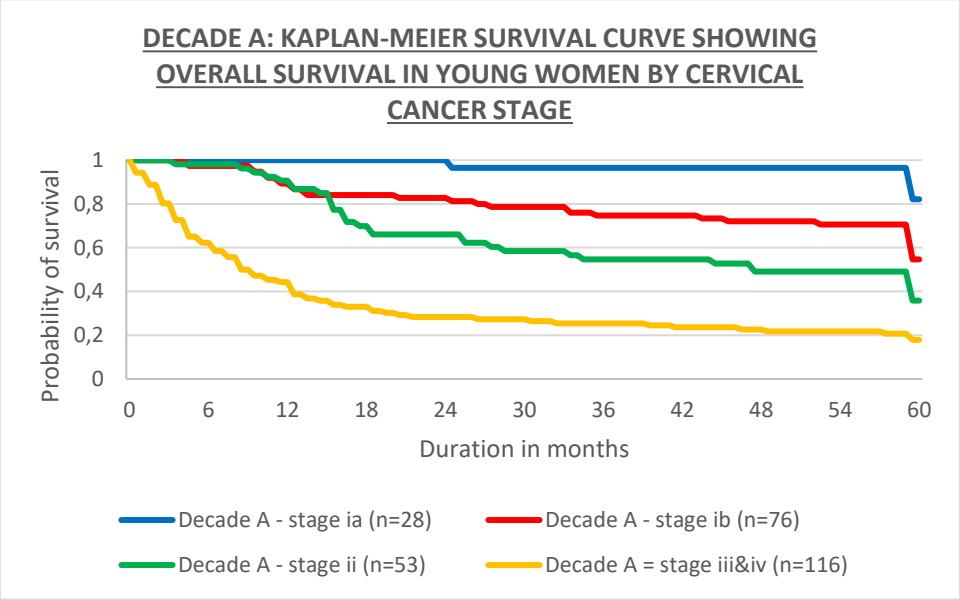


Figure 12b : Probability of survival in young women with cervical cancer, according to stage during decade B

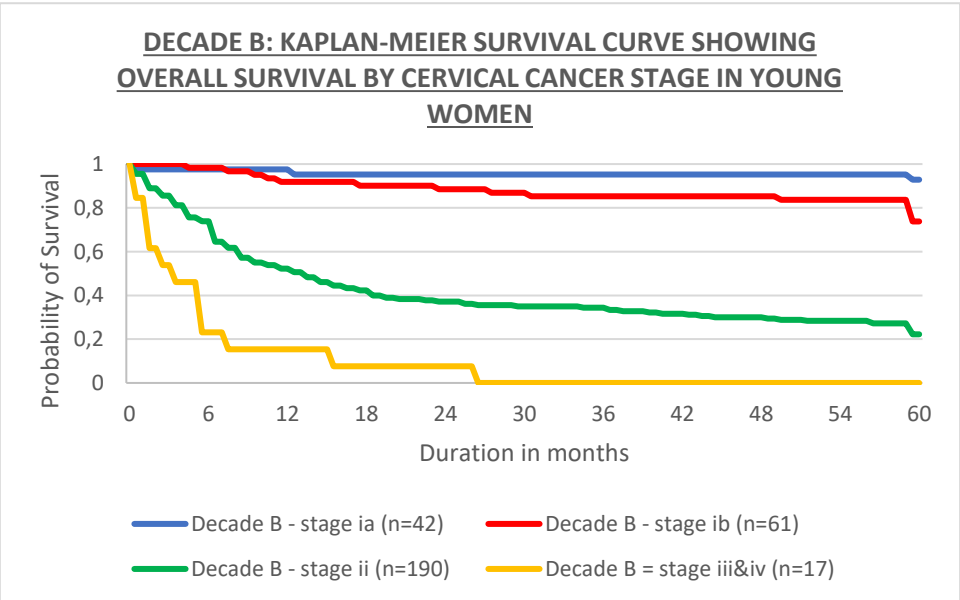


Table 9 : Mean survival in months of young women diagnosed with cervical cancer, according to stage

Stage	Decade A (n=273)	Decade B (n=310)
ia	40	59
ib	47	56
ii	48	21
iii&iv	24	3

Treatment received was analysed according to overall survival per HIV status, for each decade (Figures 13a and 13b). For this analysis, treatment was subdivided into four categories for ease of comparison, as follows – corresponding groups indicated in parentheses:

1. surgery with or without EBRT (external beam radiotherapy), adjuvant vault brachytherapy or adjuvant EBRT and vault brachytherapy (group W)
2. EBRT and intracavitary brachytherapy; chemotherapy only; vault brachytherapy or EBRT alone (group X)
3. concurrent chemotherapy (group Y)
4. palliative care (group Z)

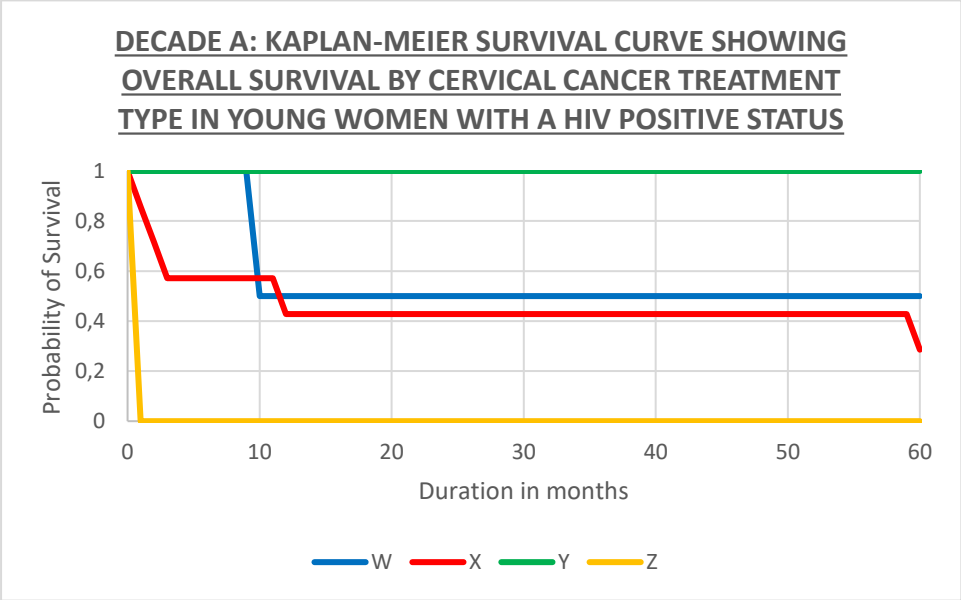
The HIV positive subset of decade A has immaterial exposures for treatment groups W, Y and Z. This results in the marked discontinuities in the graph and makes comparisons to this not credible.

During decade B, young women receiving surgery with or without radiotherapy (treatment group W), independent of HIV status, had favourable five-year overall survival outcomes relative to the other treatment groups. Those patients in this decade that were HIV positive, however, can be noted to have only a marginally worse survival outcome when compared to those with a negative status, across all treatment groups ($p>0,05$).

An improvement in survival outcomes across all durations over the five-years can be noted in decade B relative to decade A for treatment groups W and Y for HIV NP patients ($p<0,05$).

Those patients receiving treatment group Z or group X can be seen in decade B to be having the worst survival outcomes but with very similar survival trends, independent of HIV status.

Figure 13a : Probability of survival in young women with cervical cancer, according to treatment type during decade A in HIV positive and NP patients



KEY:

W - surgery with or without EBRT (external beam radiotherapy), adjuvant vault brachytherapy or adjuvant EBRT and vault brachytherapy

X - EBRT and intracavitary brachytherapy; chemotherapy only; vault brachytherapy or EBRT alone

Y - concurrent chemotherapy

Z - palliative care

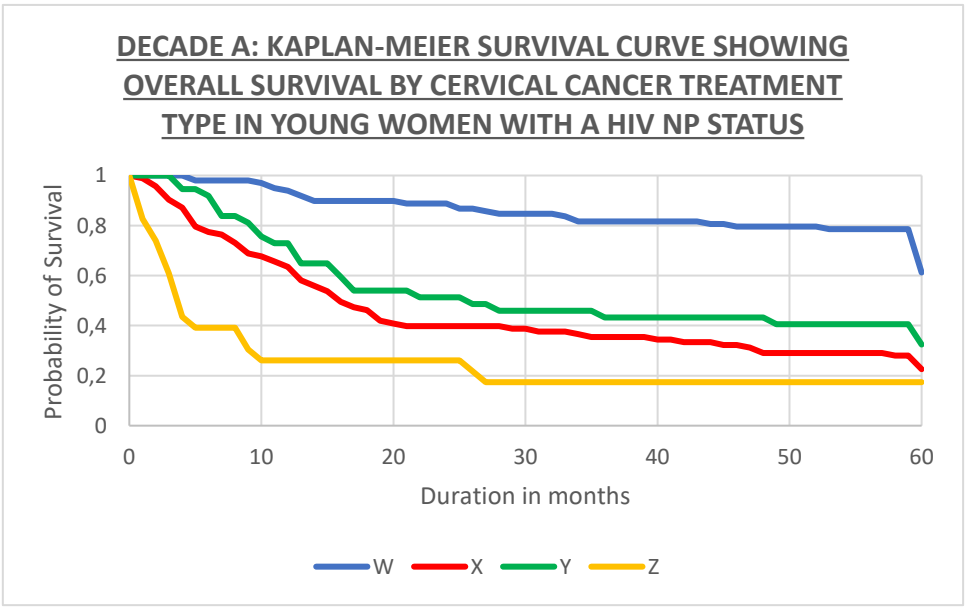
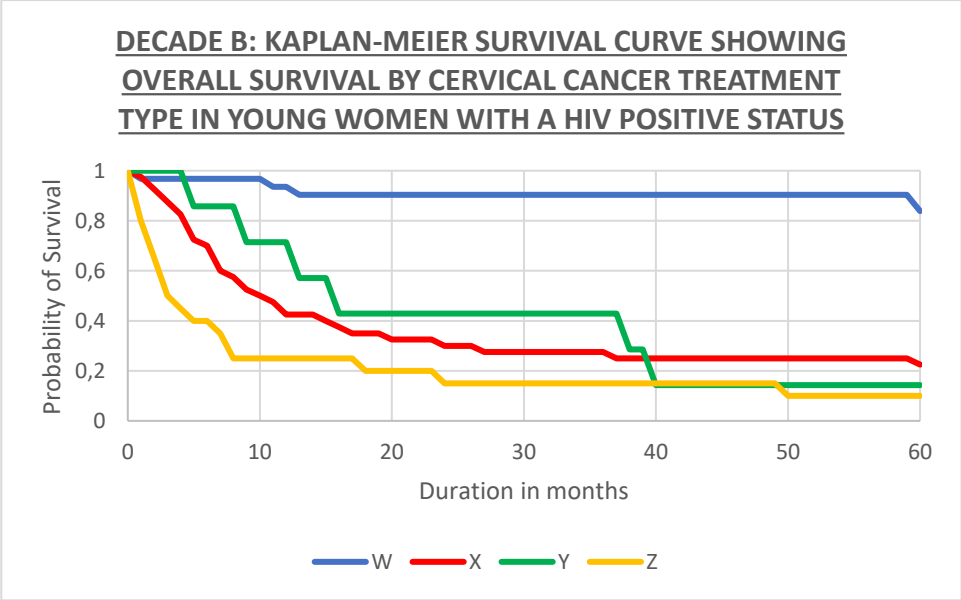


Figure 13b : Probability of survival in young women with cervical cancer, according to treatment type during decade B in HIV positive and NP patients



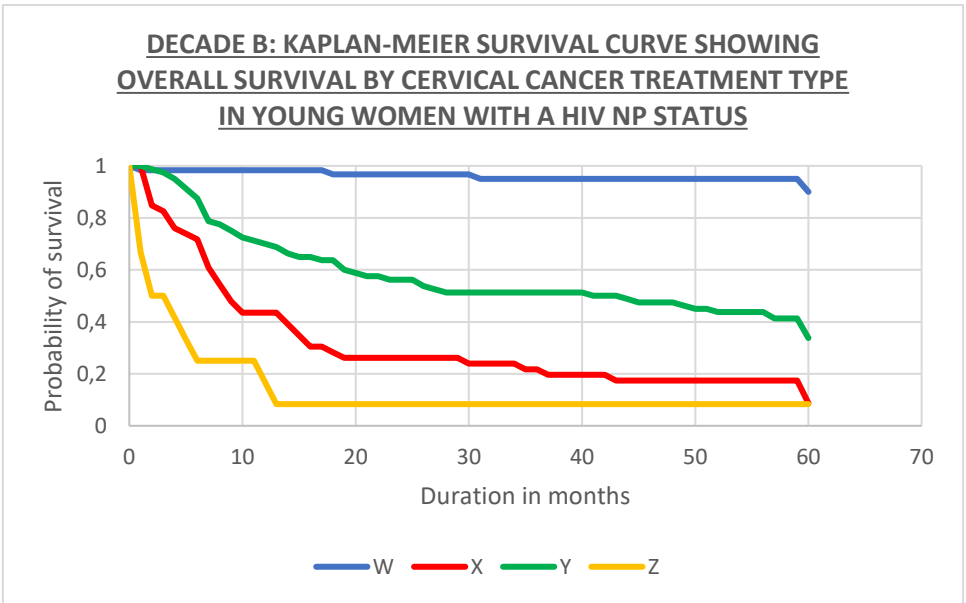
KEY:

W - surgery with or without EBRT (external beam radiotherapy), adjuvant vault brachytherapy or adjuvant EBRT and vault brachytherapy

X - EBRT and intracavitary brachytherapy; chemotherapy only; vault brachytherapy or EBRT alone

Y - concurrent chemotherapy

Z - palliative care



Despite being the second most common histological type (after squamous cell carcinoma) in this study, adenocarcinoma of the cervix is the histological subtype with the best survival probability according to the curves depicted in Figures 14a and 14b, during both decade A and B respectively. The 5-year prognosis in patients with adenocarcinoma as a histological type is usually poorer than those with squamous histology. However, despite the small cohort, from Figure 14a and 14b it appears as though patients with adenocarcinoma fared better in this study than those with squamous cell carcinoma tumours. However, the effect of histology appears to converge with duration. For each decade, there is no statistically significant difference observed between overall survival probability between the different histological types of cervical cancer (p= 0,9 for decade A and p=0,62 for decade B). When comparing the trends from decade A to decade B for each histological type, no statistically significant difference in overall survival is observed (p=0,47, p=0,14 and p=0,57 respectively for adenocarcinoma, adenosquamous carcinoma and squamous cell carcinoma).

Figure 14a : Probability of survival in young women with cervical cancer, according to histology

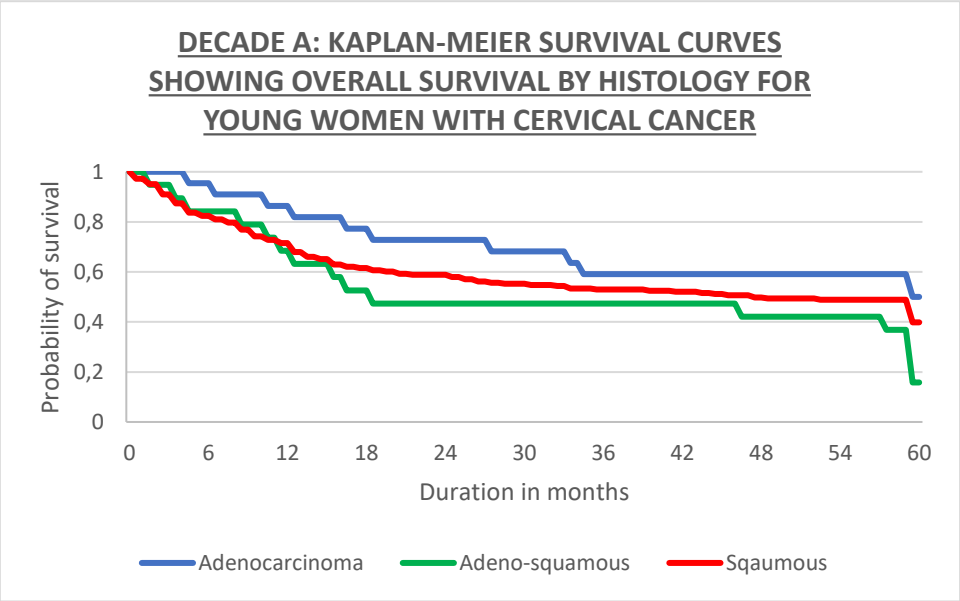
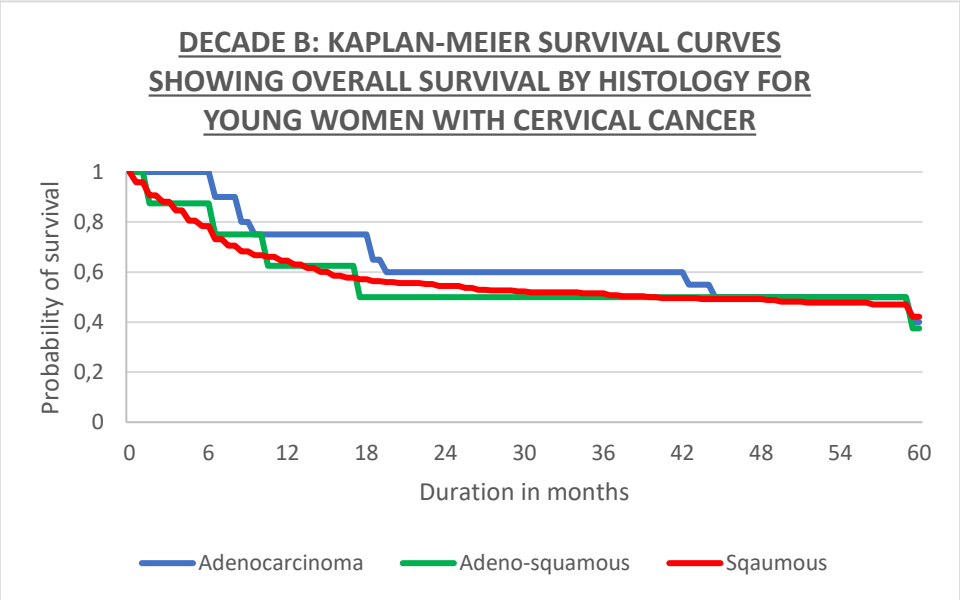


Figure 14b : Probability of survival in young women with cervical cancer, according to histology during decade B



Figures 15a and 15b depict curves for the probability of disease-free survival, according to the different early stages of cervical cancer in decade A and decade B, respectively.

There is very minimal change in the trends of disease-free survival from decade A to decade B. There is no statistically significant difference observed between the decade comparisons for each stage (p=0,24, p= 0,67 and p=0,98 respectively for stage 1a, 1b and 2).

Figure 15a : Probability of disease-free survival in young women, according to early stages of cervical cancer during decade A

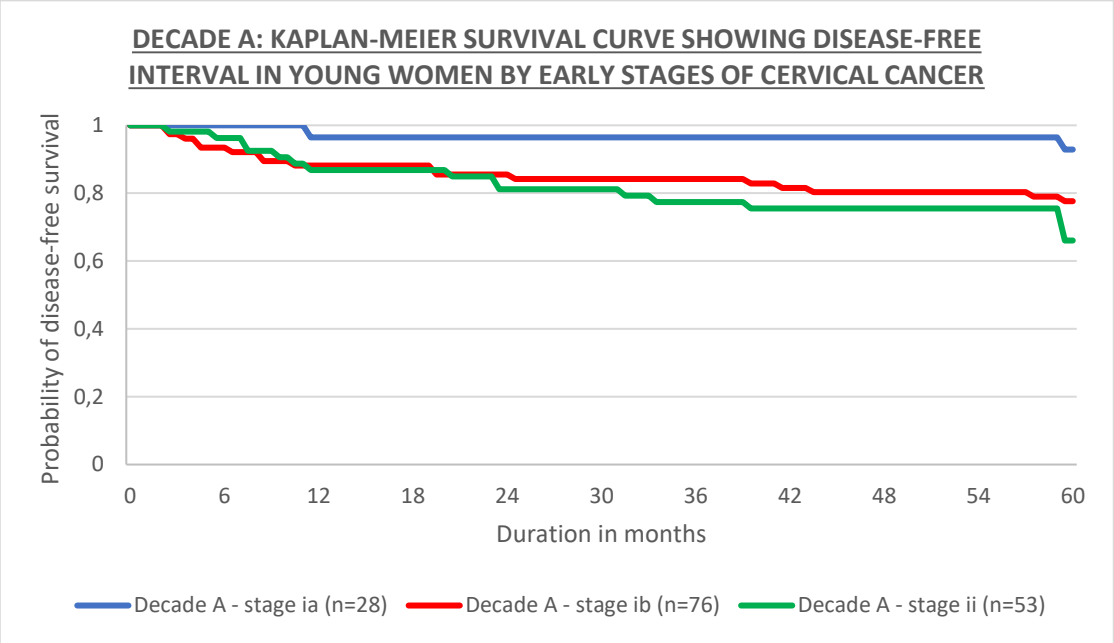
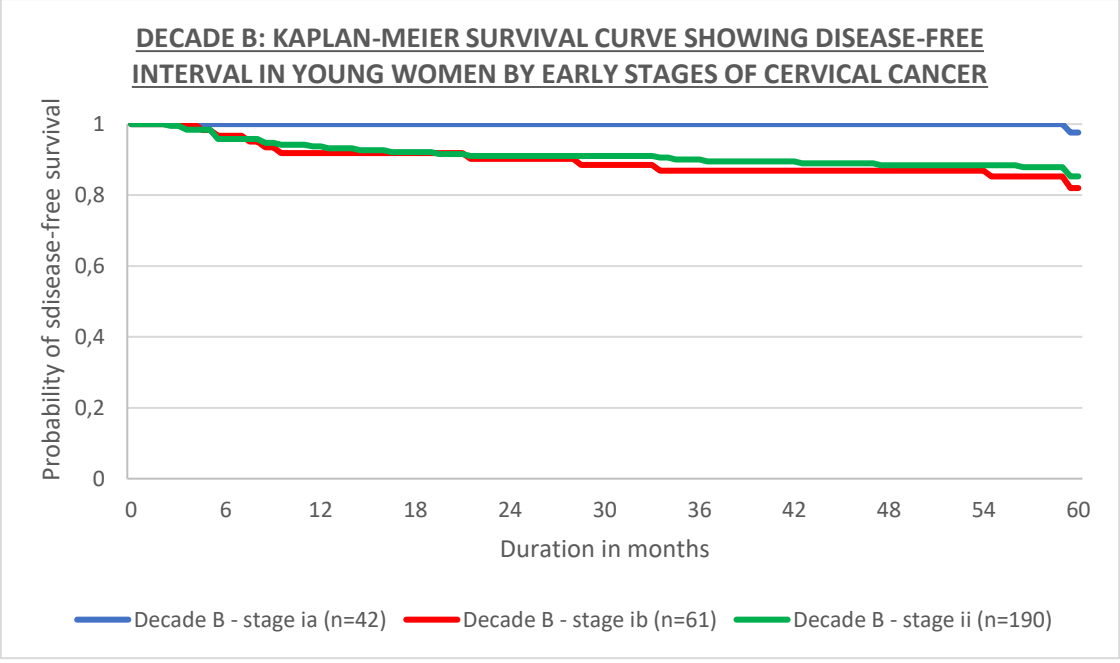


Figure 15b : Probability of disease-free survival in young women, according to early stages of cervical cancer during decade B

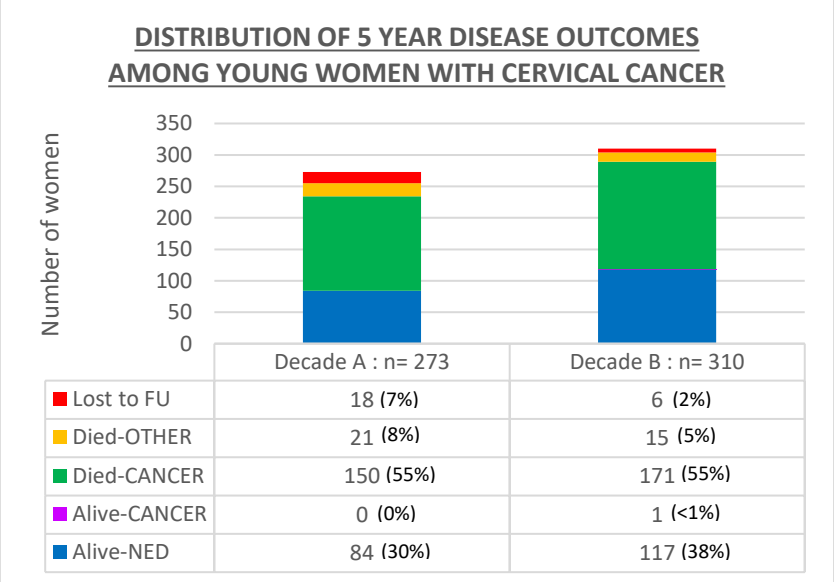


5-year disease outcome

As a parameter of an assessment of treatment outcome, the 5-year (60 months) disease status of young women diagnosed with cervical cancer was analysed.

In Figure 16, the proportion of those patients that are alive with no evidence of disease (NED) in decade A is 31% (84 patients) and 38% (117 patients) in decade B, showing no significant difference in change of trend between the decades under study (p=0,08). The proportion of patients who suffered cancer-related deaths at five years in decade A and B stayed static at 55% (150 patients in decade A and 171 in decade B). The study data do not show significant evidence that survival outcome does not differ between decades (p=0,3). Those patients that died due to other causes and that were lost to follow up were in the minority in both decades A and B.

Figure 16 : Distribution of 5-year disease outcomes among young women diagnosed with cervical cancer

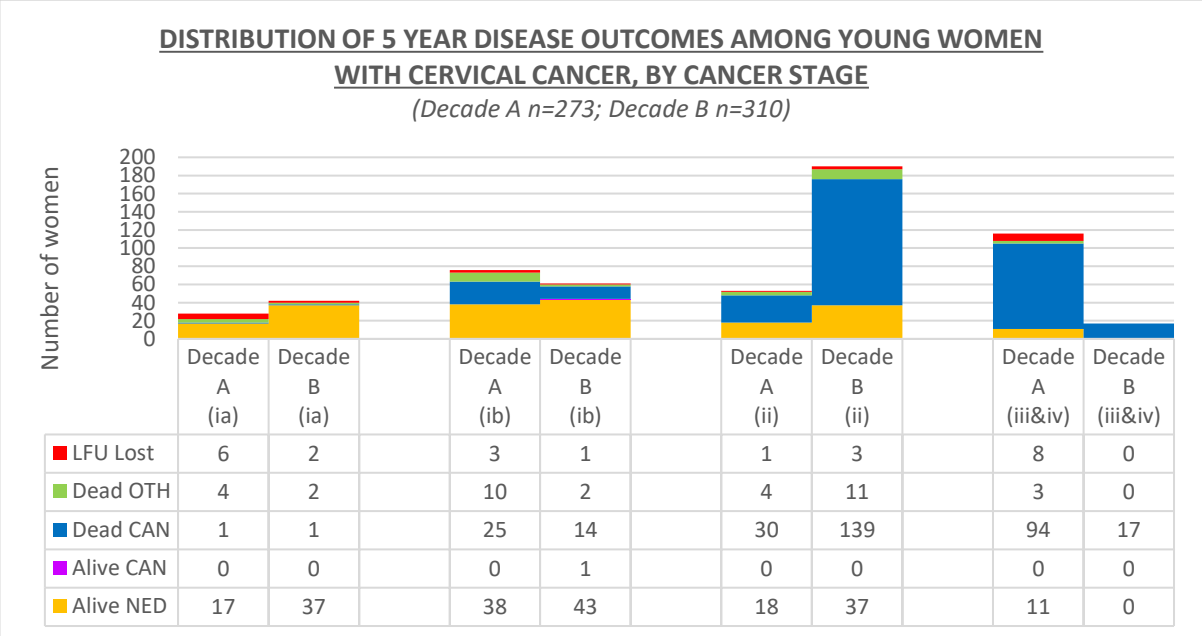


	Decade A : n= 273	Decade B : n= 310
Lost to FU	18 (7%)	6 (2%)
Died-OTHER	21 (8%)	15 (5%)
Died-CANCER	150 (55%)	171 (55%)
Alive-CANCER	0 (0%)	1 (<1%)
Alive-NED	84 (30%)	117 (38%)

Figure 17 depicts that a higher proportion of young women with early-stage cancer (stage 1a, stage 1b or stage 2) were alive with no evidence of disease at five years in decade B than in the prior decade (p=0,01). However, late-stage cancer in decade B had no survivors at 5-year follow up, compared to decade A. Death due to cancer in these young women are

noted to be markedly less with those with stage 1b, stage 3 and stage 4 cancer, during decade B than during decade A (p<0,00001). There is an increase in patients with stage 2 cancer dying from the disease in decade B (81% - 139 patients) when evaluated in contrast to decade A (20% - 30 patients), p<0,0001. This implies that more stage 2 cancer patients are dying from the disease in the more recent decade than the prior (p<0,01). As a result of clinical staging, some of the stage 2 patients could have been more advanced than clinically assessed at the first visit. The new 2018 revised FIGO staging for cervical cancer incorporates the use of CT (computed tomography) scans and MRI (magnetic resonance imaging), a move that could assist in improved staging and treatment outcomes. Type of treatments offered and received and whether treatment course was completed, would be other factors to consider as possible explanations for this finding. The proportion of patients lost to follow up across all stages of the disease, is noted to be comparable in decade A and B, signifying no better patient attendance with advancing decades.

Figure 17 : Distribution of 5-year disease outcomes among young women diagnosed with cervical cancer, according to stage of disease



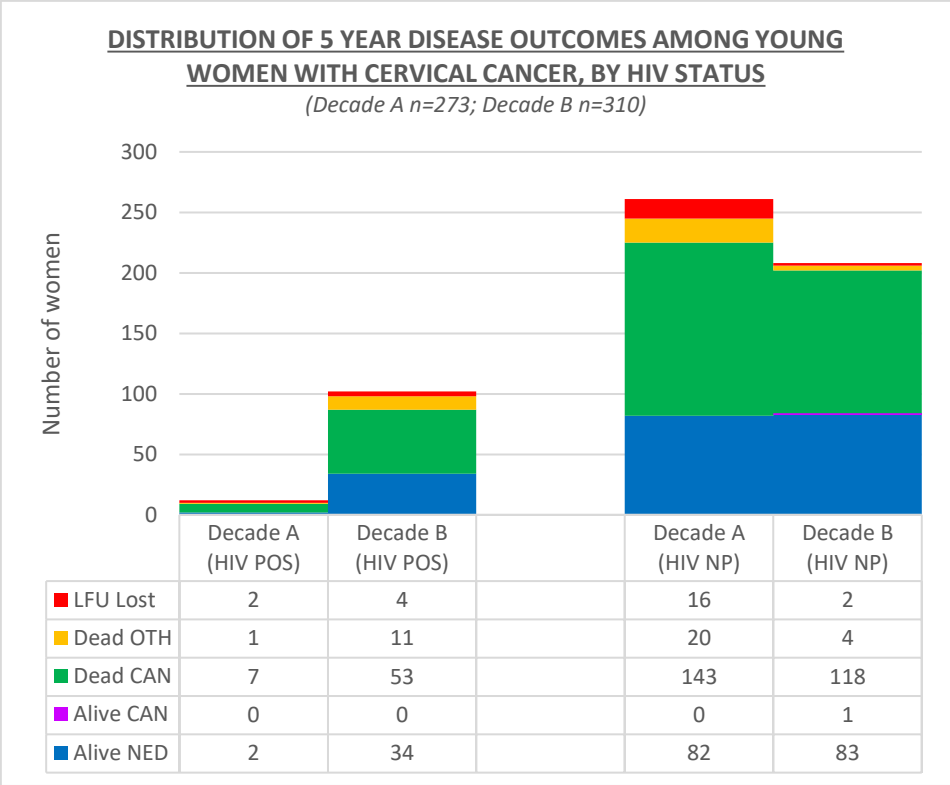
	Decade A (ia)	Decade B (ia)	Decade A (ib)	Decade B (ib)	Decade A (ii)	Decade B (ii)	Decade A (iii&iv)	Decade B (iii&iv)
LFU Lost	6	2	3	1	1	3	8	0
Dead OTH	4	2	10	2	4	11	3	0
Dead CAN	1	1	25	14	30	139	94	17
Alive CAN	0	0	0	1	0	0	0	0
Alive NED	17	37	38	43	18	37	11	0

Five-year disease outcome in young women with cervical cancer, according to HIV status, was carefully evaluated and compared between the decades under study (Figure 18). Although very few patients in decade A had HIV statuses documented, a comparison of proportions was drawn. As a result of the small sample size, results proved not credible.

There were 34 (11%) HIV positive patients and 83 (27%) HIV NP women in decade B that were alive with no evidence of disease at 60 months. HIV positive status decreases the probability of being alive with NED at 60 months (p<0,001). Comparisons between the decades were not credible due to decade A having an insufficient sample size.

Of those patients who were HIV positive, 58% (7 patients) died of cancer at five years during decade A and 52% (53 patients) during decade B. This demonstrates no significant difference between the decades (p=0,68) despite the small sample cohort in decade A. 55% (143 patients) of patients who were HIV NP had died of cancer at five years in decade A and 57% (118 patients) in decade B – this difference was noted not to be statistically significant (p=0,67). Death due to cancer at five-years was noted not to be significantly influenced by HIV status (p=0,43).

Figure 18 : Distribution of 5-year disease outcomes among young women diagnosed with cervical cancer, according to HIV status



	Decade A (HIV POS)	Decade B (HIV POS)		Decade A (HIV NP)	Decade B (HIV NP)
LFU Lost	2	4		16	2
Dead OTH	1	11		20	4
Dead CAN	7	53		143	118
Alive CAN	0	0		0	1
Alive NED	2	34		82	83

5-year survival outcome at Groote Schuur Hospital LE 33

In Table 10, the proportion of young women surviving after 5 years with stage 1 cancer, has increased from decade A (average of 56%) to B (average of 80%). This is quite comparable to the FIGO statistics in Table 2, where, across all age groups, the average 5-year survival is 89% in stage 1 women. For those in this study with stage 2 cervical cancer, 5-year survival has decreased from 34% in decade A to 19% in decade B (corresponding average FIGO 5-year survival in Table 2 of 70%). This is a marked decrease, not comparable to international standards. The 5-year survival for late-stage cancer patients has decreased from 9% during decade A to no survivors documented during decade B – this compared to an international average of 28% as per the FIGO 5-year survival in Table 2 for this subset of women.

Table 10 : Percentage of young women (40 years and younger) alive after 5 years, according to each decade

Stage	% women alive after 5 years	
	Decade A	Decade B
1a	61%	88%
1b	50%	72%
2	34%	19%
3 and 4	9%	0%

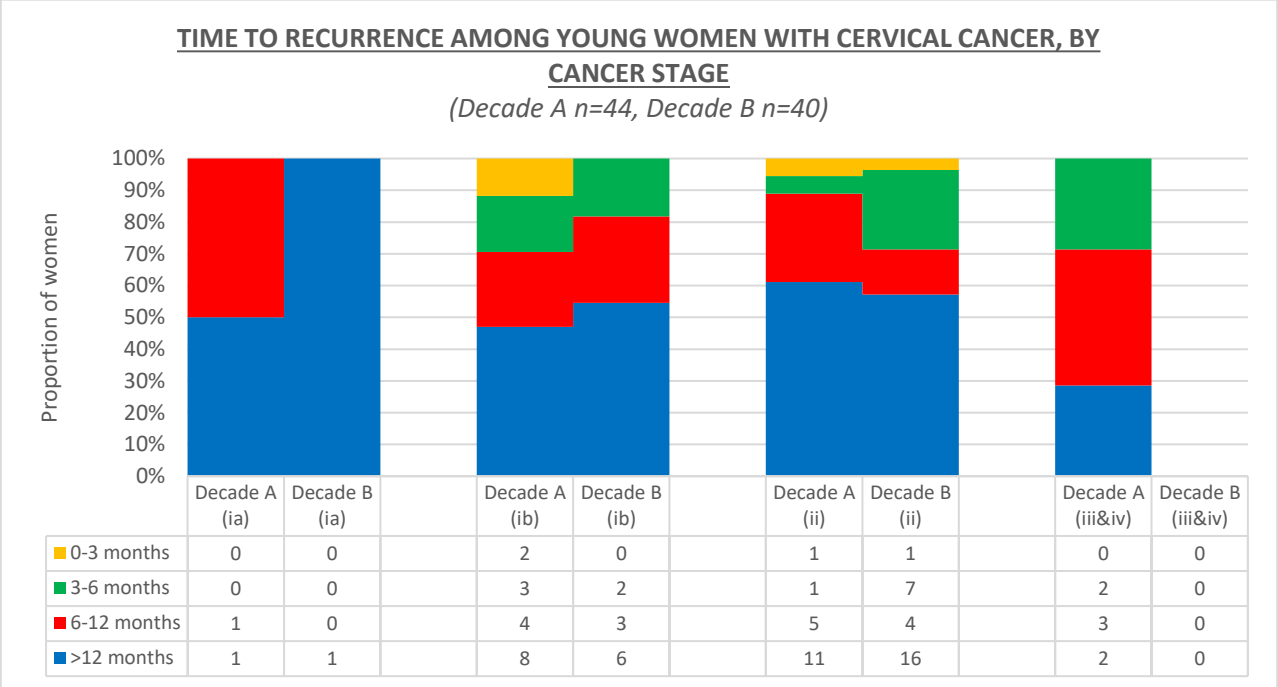
Time to recurrence

In those patients with early-stage cervical cancer, time to recurrence was measured from the end date of treatment instituted, to the date of relapse of cervical cancer. This analysis, therefore, only included those patients who had relapsed. Figure 19 shows a comparison of this time in each decade according to stage and HIV status.

Figure 19 shows that an improvement can be seen in time to recurrence for stage 1a patients with all patients in decade B not relapsing within 12 months (approximately 50% in decade A relapsed within 12 months). Young women with cervical cancer stage 1b in decade B also seem to be taking longer to recur compared to the previous decade. However, when tested the proportion of stage 1a and 1b relapses has not significantly improved from decade A to decade B (p=0,31).

When comparing the young women diagnosed with stage 2 cancer during decade A and B, the proportion of patients during decade A taking 3 months and less to recur, and those taking six to twelve months to recur, have not reduced significantly to the proportion depicted in decade B (p=0,23). The proportion of stage 2 patients recurring by 12 months or more during decades A and B differ only marginally. There is a statistically significant increase in the proportion of patients with stage 2 cancer from decade A to decade B who are taking three to six months to recur (p=0,04).

Figure 19 : Time to recurrence among young women with cervical cancer, by stage

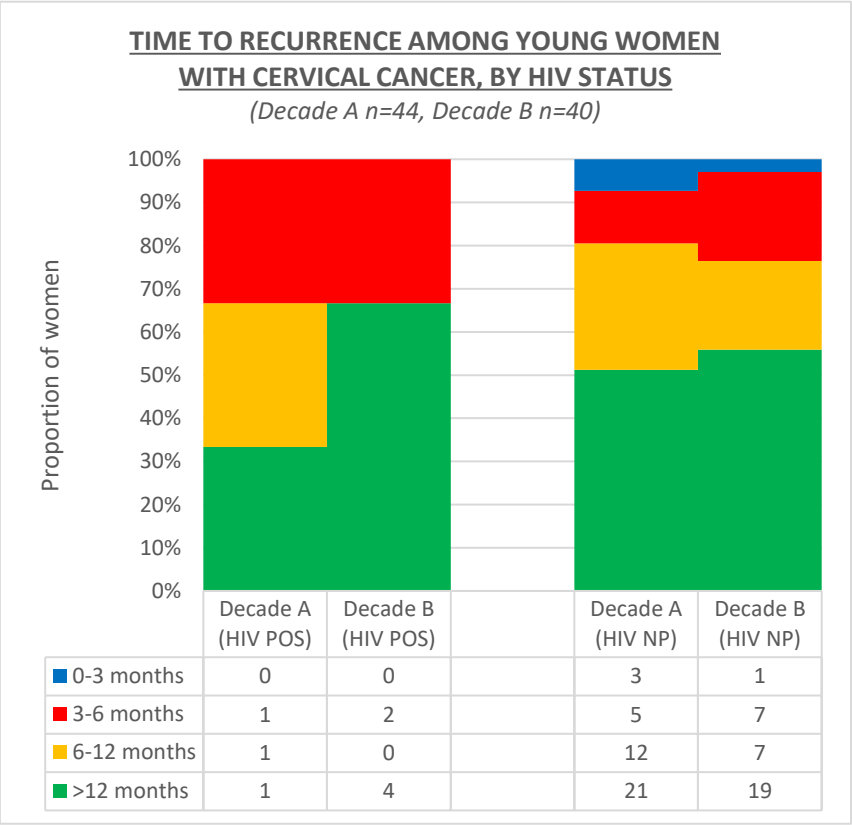


	Decade A (ia)	Decade B (ia)	Decade A (ib)	Decade B (ib)	Decade A (ii)	Decade B (ii)	Decade A (iii&iv)	Decade B (iii&iv)
0-3 months	0	0	2	0	1	1	0	0
3-6 months	0	0	3	2	1	7	2	0
6-12 months	1	0	4	3	5	4	3	0
>12 months	1	1	8	6	11	16	2	0

Figure 20 displays the different time intervals to recurrence, according to patients who are HIV positive compared to those HIV NP, in each decade. An improvement can be noticed from decade A to decade B in those patients who are HIV positive, as the proportion of patients recurring during 6 – 12 months in decade A, improve to a later time to recurrence of 12 months or more in decade B, however, this finding proved not to be statistically significant (p=0,34).

In decade B's HIV NP cohort, there is an increase in the proportion of individuals taking 3 – 6 months and 12 months and more, to recur. In this same subset of women, those taking less than 3 months and 6 – 12 months to recur have decreased in quantity. However, due to the small relapse sample size in this study, these trends cannot necessarily be extrapolated to the population (p=0,22).

Figure 20 : Time to recurrence among young women with cervical cancer, by HIV status



	Decade A (HIV POS)	Decade B (HIV POS)		Decade A (HIV NP)	Decade B (HIV NP)
0-3 months	0	0		3	1
3-6 months	1	2		5	7
6-12 months	1	0		12	7
>12 months	1	4		21	19

Discussion

Approximately, one-fifth of all cervical cancer patients diagnosed during a ten-year period at GSH will affect young women forty years and younger. Of this group, about 17% on average will be thirty years and younger while the majority will be between thirty-one and forty years of age.

The two decade-groups under study showed no difference in trend with regards to age: survival between the older age group and the younger age group of women with cervical cancer during decade A and B showed no noteworthy difference. No substantial difference in overall survival exists between the young population in both decades.

There was no evidence to suggest that overall survival is dependent on the histological type. However, the sample cohort was not large enough to show the variation in the trend between the decades.

Initial Hb at presentation in women 40 years and younger, showed no change in trend from decade A to B – however, this was the Hb level recorded at the first LE 33 visit and no further data was extracted to examine if patients had received prior transfusions of iron supplementation.

Decade B showed more early-stage cancer than decade A. In this early-stage cervical cancer cohort, there is a trend toward more locally-advanced (stage 2) cancers in the more recent decade. The SA National cervical screening initiative rolled out in the year 2000, with the "30-40-50" routine pap smear screening rule brought into effect. This could account for the increase in the early-stage cancer identification and diagnosis rate that can be seen from decade A to decade B in this population subset. However, even though the number of early-stage cancers detected has increased with subsequent decades, it is worrying to note that it is not the quantity of stage 1 disease that has climbed, but rather the proportion of stage 2 cancers that have increased. This raises concern as it seems as if early stage 1 cancers, that could have possibly been detected by cytological abnormalities on a simple Pap smear are now going on to develop later-stage cancer before presenting to a healthcare institution. Alternatively, due to the decrease in the number of late-stage disease presenting in these young women during decade B, it is also possible that more late-stage disease is actually being detected at an earlier phase as stage 2 disease. This could possibly be due to the ’30-40-50’ pap smear roll-out initiative, encouraging women to present themselves earlier to a healthcare institution. Further in-depth investigation to uncover the exact contributing factor for the rise in stage 2 disease is needed to clarify the results.

Currently, approximately 75% of women in developed countries have had some type of cervical cancer screening within the last 5 years, in contrast to less than 5% of women in the developing world.[34] Thus, emphasis needs to be placed on screening young women – not only just screening but also screening of the correct population at the appropriate time is of vital importance. While cytological screening has lowered the incidence of invasive cervical cancer in many developed countries, this type of screening needs established laboratory services, trained pathologists, and a minimum of three visits for screening, review of abnormal cytology results and subsequent treatment thereof. In these low-resource environments, this strategy has proven difficult to implement and sustain.[35,36,37] In such countries with limited resources, multiple alternatives to cytological testing is available – cervicography, VIA, VILI, DVI, HPV-testing as well as co-testing.[38] Closer investigation into screen-and-treat options (e.g. cryotherapy after a VIA positive test result) for low-resource settings have proved widely beneficial and is an efficient and cost-effective manner in which to manage patients.[39]

Regarding staging and markers of 'aggression' for cervical cancer, there has been a notable approximate 50% decrease in the proportion of patients presenting with early-stage 1a and 1b cancer with tumours 4 cm and less from decade A to decade B. This specific subset of patients, allows for preferred surgical management. Surgery is superior to radiotherapy (either as a primary or adjuvant treatment) in this category of women, as they are still in their reproductive years, and by avoiding pelvic-radiation exposure their ovarian reserve and function can be preserved. However, with the decrease observed with the progressing decades – it seems that fewer patients get to use this ovarian-sparing management option.

There has been a significant increase in the proportion of stage 2 cancers presenting with tumours 2 – 4cm in size in decade B; almost 3-fold that of decade A. There is a shift in the trend of the majority of young women, from smaller tumours (2cm or less) seen in decade A to tumours 2 to 4 cm in size in decade B. This could point to a developing trend of presentation of both, more locally-advanced and slightly larger tumour size in early-stage cancer rather than more stage 1 early-stage microscopic disease presenting.

The proportion of women with late-stage cancer with and without hydronephrosis did not demonstrate any significant change in trend from decade A to decade B. The mean overall survival in patients with late-stage cancer and hydronephrosis has also not changed from decade A to decade B: the mean survival in stage 3b patients at approximately 1 year and in those stage 4 patients at approximately three and a half months on average, versus 28 months and 6 months respectively for the equivalently staged patients without hydronephrosis.

The subset of young women with late-stage cancer and unilateral parametrial involvement decreased. In contrast, bilateral parametrial involvement and PSW invasion had significantly increased from decade A to decade B. The mean overall survival in patients with parametrial involvement (unilateral and bilateral) as well as in patients with pelvic sidewall invasion, have had no change in trend from decade A to decade B – those with PSW involvement having the best mean survival at approximately 54 months on average.

With reference to the type of treatment received during decade A, the majority of patients received treatment group 1 (surgery with or without EBRT, adjuvant vault brachytherapy or adjuvant EBRT and vault brachytherapy). The majority of patients in decade B however, received concurrent chemotherapy (treatment group 4), followed by treatment group 1. This shows the evident shift in management from the year 1999 onwards, where young women with cervical cancer in decade A, received mainly radiotherapy without chemotherapy, to decade B where patients received a combination of radiotherapy and chemotherapy.

As cervical cancer treatment is stage-dependent, the majority of stage 1 disease in both decades received treatment group 1. Significantly more women in decade B with stage 2 cancers received treatment group 2 or 4 compared to decade A, most likely due to the increase in the incidence of stage 2 cancers and the shift in management from radiotherapy alone to combined chemoradiation that occurred more so in the latter decade.

Those patients who received treatment group W (surgery with or without radiotherapy) had the best probability of survival, followed by treatment group Y (concurrent chemotherapy) - attributed to the fact that the majority of early-stage cervical cancer fell into these two treatment groups. As alluded to earlier, treatment of stage 1 and some stage 2a cervical cancer is usually surgical (treatment group W) unless there are contraindications to surgery, which is when primary chemoradiation (treatment group Y) then becomes the treatment of choice in these patients. The different types of surgery can range from a cone biopsy for early-stage 1a disease to a radical hysterectomy (removal of the uterus, cervix, parametria and vaginal cuff) with bilateral pelvic lymph node dissection of the external iliac, internal iliac, obturator, and common iliac lymph nodes.[40] Fertility-sparing options for surgery has become increasingly more common in the surgical treatment of early-stage disease (such as cone biopsy, trachelectomy or radical trachelectomy) for selected young individuals and with good results.[41] However, patients who do not fulfil the criteria to be surgical candidates will then receive combined chemoradiation treatment. The addition of chemotherapy to radiotherapy offers a reasonably significant benefit on all outcomes (including survival, disease-free survival, local and distant recurrence as well as side effect profile) and for all stages of disease.[42] Thus, the evidence-based change in trend from radiotherapy alone in this group of women to combined chemoradiation that can be seen from decade A to decade B. This particular subset of women are in their reproductive years, and with many

women wanting to start families at a later age, fertility-sparing options to preserve fertility as far as possible is important. Standard pelvic radiation doses can cause ovarian ablation, but oophoropexy (ovarian transposition) can assist with the preservation of fertility and ovarian function in such cases.[43]

During both decades and across all durations (up to 60 months), stage 1 cervical cancers had the best probability of survival. Mean survival also improved in this subset - an average of 44 months during decade A to 58 months during decade B. Although, there was no difference in overall survival in those young women with stage 2 cancer from decade A to B, there is a noteworthy deterioration in mean survival in these patients from 48 to 21 months in decade A to B, respectively. Late-stage cancer had the worst overall survival with no change in trend from decade A to B, with mean survival noted to have dropped from 2 years in decade A to 3 months in decade B.

Practically no difference in disease-free probability existed between each stage of cancer: 1a, 1b and 2. Disease-free probability of survival for these early-stage cancers showed no difference between the decades either.

There is no evidence of change in the proportion of patients during decade A that are 'alive with NED' and that 'died of cancer' when compared to that in decade B. However, the study data did not show significant evidence that survival outcomes do not differ between the decades under analysis. A higher proportion of young women with early-stage disease were alive with NED at 60 months during the later decade. Decade B also fared better with the number of patients suffering from cancer-related deaths decreasing in those with stage 1b and late-stage cancers. However, stage 2 patients during decade B did worse than during decade A, as a higher proportion of women suffered cancer-related deaths during decade B.

This study demonstrated that time to recurrence in decade B when compared to decade A for stage 2 cancer patients, has increased in the 3 – 6 months category - indicating a deterioration, as more patients in the more recent decade are now taking a shorter interval to relapse than in the prior decade.

When viewed in comparison to the FIGO statistics, stage 1 Groote Schuur Hospital cervical cancer patients seem to be in keeping with international 5-year survival trends. Our institution's stage 2 and late-stage cancer patient's 5-year survival trend has proven poorer with evidence of deterioration with the decades.

Due to HIV testing only becoming a standard and routine practise during decade B (evidenced by a third of this population being HIV positive and 59% HIV negative), the majority of the HIV comparisons during decade A proved not credible.

There is not enough convincing evidence in the data to show a difference in overall survival outcomes based on HIV status, for both decades under study. Mean survival in both HIV positive and NP women has decreased from decade A to decade B. Nevertheless, patients with a NP status have better mean survival than those that are status positive during both decades. HIV positive status was shown in this study to have decreased the probability of being alive with NED at 60 months significantly. Cancer-related deaths at 5 years are independent of HIV status.

It was interesting to note that tumour size on presentation (for tumours less than 4 cm) in the latter decade, was influenced by HIV status. However, comparisons between HIV status and time to recurrence proved challenging to analyse constructively due to the small relapse sample size in this study, and hence these trends cannot necessarily be extrapolated to the population.

Conclusion

Although this study concentrated on a minimal subset of the total cervical cancer population (approximately 20%), it is this crucial cohort of women that represent young patients in their prime reproductive and adult years. With cervical cancer being a potentially curable disease if presented timeously, this specific group of patients should be the focus of primary and secondary prevention strategies.

This study demonstrated that there is a trend toward the diagnosis of more locally-advanced (stage 2) cervical cancer in young women, with worsening survival outcomes in the more recent decade. As the majority of staging was clinical, some stage 2 cancer patients could likely have been under-staged and could have been more advanced at the time of initial clinical assessment. The new 2018 revised FIGO staging for cervical cancer incorporates the use of CT (computed tomography) scans and MRI (magnetic resonance imaging), a move that could assist in improved staging and treatment outcomes. This finding ultimately indicates that more strategic efforts need to be focussed on primary and secondary preventative strategies to try and identify patients at an earlier point in time where they will have better overall survival and disease-free outcomes and in-turn assist with curbing the rising cervical cancer morbidity and mortality. Since the roll-out of the HPV vaccine in 2014 to school-going girls in South Africa, the effect of this primary preventative strategy on the incidence of cervical cancer is yet to be assessed.[4]

This study seemed to show that there is a possible link between tumour size at presentation and HIV status, as well as a decreased probability of disease-free survival at 5 years if status positive. As the association between HIV and invasive cervical cancer is complex, additional details and information are needed to clarify these findings. HIV-positive women are up to five times more likely to be at risk for developing cervical cancer compared to those with a negative status.[44] Knowing this, presents healthcare workers with a powerful opportunity for the development of a life-saving alliance between two critical global health burdens. By combining the approach to address both HIV and cervical cancer, potentially holds many significant benefits, of which the roll-out of the HPV vaccine is only a start. With the furthering success of ARV treatments and advances in HIV care, a critical opportunity exists to increase knowledge and raise awareness of symptoms, signs and risks of cervical cancer, promotion of safe-sex practices, knowing one's status and emphasizing the importance of getting tested as well as screening for cervical cancer at regular intervals.

The analysis and review done in this retrospective audit lead the author to believe that a more focussed screening programme will prompt earlier diagnosis with subsequent appropriate and timeous treatment of cervical cancer, together with optimisation of comorbidities like HIV in this group of young patients will aid the burden of this potentially curable disease in this specific subset of young women.

Acknowledgements

The author expresses thanks and acknowledgement to the CEO of GSH, the LE 33 unit HOD and the late Dr Leon Van Wijk for allowing the author access to the files and database and permission to conduct the study at this institution. Dr Van Wijk had initially started, compiled and was regularly updating the cervical cancer database for the LE 33 unit – which forms the foundation of this entire study.

The author is particularly grateful for the apt advice, professional guidance, valuable support, constructive recommendations and assistance given by the research supervisors, Dr Nomonde Mbatani and Dr Nazia Fakie, along this journey. There was no conflict of interest declared in this study from any of the authors and supervisors.

The author extends special thanks to her brother, Purishlin Govindasamy (B Com Hons [Actuarial Science] (Stell), CFP®, AMASSA, CERA) who tirelessly studied, examined, tested, tabulated and graphically analysed the data.

Finally, the author wishes to thank her family for their unwavering support and encouragement throughout her study - it is genuinely appreciated.

Strengths, Limitations and Recommendations

The strength of this study was the comparison between decades of outcomes and 5-year survival trends. This study, however, fell short in the fact that it was a retrospective audit and data obtained was occasionally missing or incomplete from the pre-existing database and CAC registration forms. The sample size was small, the study time-period was short, and the audit conducted at only one institution in the Western Cape. Due to the small sample size, different cancer stages were grouped together (eg. stage 2 rather than stage 2a and stage 2b) rather than analysed separately which would have yielded better information. Radiotherapy techniques have also improved with the passing of decades, which could have also had an impact on the outcomes demonstrated in this study. In this study, comparisons between the HIV positive cohort of patients to those grouped as 'not positive' (inclusive of HIV negative patients, untested patients and those patients with undocumented test results) could have possibly skewed data, especially if those patients in the latter were HIV positive. The author, therefore, recommends that these comparisons and trends be more accurately and closely examined as part of a larger, multi-centred, and national analysis to better clarify these findings confidently before extrapolating it to the population.

Further finer details with reference to HIV (details of diagnosis, treatment regimens and viral load levels and trends), Hb (the level at first presentation to a healthcare facility, details of blood transfusions and oral or intravenous iron supplementation), Pap smear (date of the last test done and if the patient received the result), other risk factors (smoking, age at sexual debut, number of sexual partners, type of contraceptive use), late-stage disease (reasons why these patients present so late, their risk factors present, their follow-up course and how their quality of life fare) and treatment (type, side-effects, diagnosis-to-treatment time, duration of treatment received) are all critical details that would give more information and clarity to some aspects only touched upon in this study. Nonetheless, the findings in this small retrospective audit offer further hypothesis-generating data and serve to emphasize the importance of considering disease distribution, significant comorbidities like HIV status, the stage of cancer, tumour size and histology when determining 5-year survival and disease-free outcomes in young women.

References

1. Botha H, Cooreman B, Prof Dreyer G, et al. Cervical cancer and human papillomavirus: South African guidelines for screening and testing. South Afr J Gynaecol Oncol. 2010;2(1):23-26.

2. Wang-Shick Ryu. Molecular Virology of Human Pathogenic viruses. 2017 <https://www.sciencedirect.com/topics/neuroscience/dna-viruses>

3. Kahn JA. HPV vaccination for the prevention of cervical intraepithelial neoplasia. N Engl J Med. 2009; 361:271.

4. Delany-Moretiwe S, Kelley KF, James S, et al. Human Papillomavirus Vaccine Introduction in South Africa: Implementation Lessons From an Evaluation of the National School-Based Vaccination Campaign. Glob Health Sci Pract. 2018;6(3):425-438. Published 2018 Oct 4. doi:10.9745/GHSP-D-18-00-90

5. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999; 189:12.

6. Ries LAG, Melbert D, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2004. National Cancer Institute; Bethesda, MD 2007

7. Bray F, Ferlay J, Soerjomataram I, et al. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA : A Cancer Journal for Clinicians. 2018;68:394–424

8. Chang, Chung, et al. Determining the Optimal Number and Location of Cutoff Points with Application to Data of Cervical Cancer. Public Library of Science: April 2017, 12(4): p. e0176231.

9. Anorlu RI. Cervical Cancer: The Sub-Saharan African Perspective. Reproductive Health Matters. 2008;16(32):41-9.

10. Public Health England: Quarterly Cervical Coverage Report: <https://digital.nhs.uk/data-and-information/publications/statistical/cervical-screening-programme/cervical-screening-programme-england-2016-17>

11. Pillay AL. (2002). Rural and Urban South African Women's Awareness of Cancers of the Breast and Cervix. Ethnicity & Health, 7(2): 103.

12. Young RC. Cancer care in women: will the practice of the 20th century be relevant in the 21st? (Presidential address: International Gynecological Cancer Society). Int J Gynecol Cancer 2001; 11: 1–8.

13. Cooper D, Morroni C, Orner P, Moodley J, Harries J, Cullingworth L, Hoffman M. (2004). Ten Years of Democracy in South Africa: Documenting Transformation in Reproductive Health Policy and Status. Reproductive Health Matters, 12(24): 70-85.

14. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep 1992;41:1-19.

15. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. CA Cancer.

16. Centre fro Disease Control. <https://www.cdc.gov/cancer/cervical/basic_info/screening.htm>

17. National Cancer Institute. <www.cancer.gov/types/cervical/pap-hpv-testing-fact-sheet>

18. Sankaranarayanan R, Gaffikin L, Jacob M, Sellors J, Robles S. A critical assessment of screening m ethods for cervical neoplasia. Int J Gynaecol Obstet. 2005: 89 (Suppl 2):S4–S12.

19. Botha MH, Richter KL. Cervical cancer prevention in South Africa: HPV vaccination and screening both essential to achieve and maintain a reduction in incidence. South African medical journal. 2015; 105(1): 33-4.

20. The South African Society of Obstetricians and Gynaecologists. <https://www.sasog.co.za/images/sasog_screening_for_cervical_cancer_november_final.pdf>

21. Statistics South Africa <https://www.statssa.gov.za/publications/P0302/P03022018.pdf>

22. Clarke B, Chetty R. Postmodern Cancers: the role of HIV in uterine cervical cancer. Mol Path 2002;55:19-24.

23. Wang C et al. Rapid rise in detection of human papillomavirus (HPV) infection soon after incident HIV infection among South African women. J Infect Dis. 203(4):479-86, 2011.

24. World Health Organization. <https://www.afro.who.int/health-topics/cervical-cancer>

25. Yang YC, Shen J, Tate JE, et al. Cervical cancer in young women in Taiwan: prognosis is independent of papillomavirus or tumor cell type. Gynecol Oncol. 64:59–63. 1997.

26. Rivard C, Stockwell E, Yuan J, et al. Age as a prognostic factor in cervical cancer: A 10 year review of patients treated at a single institution. Gynecologic Oncology. 2016, 141, 2-208.

27. Cao L, Li X, Zhang Y and Wang Q. Clinical features and prognosis of cervical cancer in young women. J Central South Univ (Med Sci). 35:875–878. 2010.

28. Wang J et al. Patient age, tumor appearance and tumor size are risk factors for early recurrence of cervical cancer. Molecular and Clinical Oncology. 2015 Mar; 3(2): 363–366.

29. Prof Michael C Herbst, Cancer Association of South Africa (CANSA) Fact Sheet on Cervical Cancer, Oct 2011.

30. Pelkofski E, Stine J, Wages NA, et al. Cervical Cancer in Women Aged 35 years and Younger. Clinical Therapeutics. Vol 38, no 3, pp459-466, 2016.

31. Quinn MA, Benedet JL, Odicino F, et al. Carcinoma of the cervix uteri. Int J Gynaecol Obstet. 2006; 95:S43.

32. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med. 1999;340(15):1144-1153. doi:10.1056/NEJM199904153401502

33. Todo Y, Watari H. Concurrent chemoradiotherapy for cervical cancer: background including evidence-based data, pitfalls of the data, limitation of treatment in certain groups. Chin J Cancer Res. 2016;28(2):221-227. doi:10.21147/j.issn.1000-9604.2016.02.10.

34. Denny L, Quinn M, Sankaranarayanan R. Screening for cervical cancer in developing countries. Vaccine. 2006 Aug 21;24:S71-7.

35. Pisani P, Parkin DM, Ferlay J. Estimates of the worldwide mortality from eighteen major cancers in 1985: Implications for prevention and projections of future burden. International journal of cancer. 1993 Dec 2;55(6):891-903.

36. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. International journal of cancer. 1999 Mar 15;80(6):827-41.

37. Kitchener HC, Symonds P. Detection of cervical intraepithelial neoplasia in developing countries. The Lancet. 1999;353(9156):856-7

38. Denny L, Kuhn L, Pollack A, Wainwright H, Wright Jr TC. Evaluation of alternative methods of cervical cancer screening for resource-poor settings. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2000 Aug 15;89(4):826-33.

39. Denny L, Kuhn L, De Souza M, Pollack AE, Dupree W, Wright TC. Screen-and-treat approaches for cervical cancer prevention in low-resource settings: a randomized controlled trial. Jama. 2005 Nov 2;294(17):2173-81.

40. Petignat P, Roy M. Diagnosis and management of cervical cancer. Bmj. 2007 Oct 11; 335(7623): 765-8.

41. Abu-Rustum NR, Sonoda Y. Fertility-sparing surgery in early stage cervical cancer: indications and applications. J Natl Compr Canc Netw. 8(12):1435-1438, 2010.

42. Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC) 2010 Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis Cochrane Database of Systematic Reviews.

43. Tulandi, Togas et al. Laparoscopic ovarian suspension before irradiation, Fertility and Sterility, Volume 70, Issue 2, 381 - 383.

44. FIGO News. 2018. <www.figo.org/news/cervical-cancer-and-hiv>

45. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. CA Cancer J Clin 2012; 62:147.Curry SJ. Screening for cervical cancer: United States Preventive Services Task Force recommendation statement. JAMA 2018; 320:674.

46. Cervical cytology screening. ACOG Practice Bulletin No. 157. American College of Obstetricians and Gynecologists. Obstet Gynecol 2016; 127:e1

47. Huh WK, Ault KA, Chelmow D, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: Interim clinical guidance. Gynecol Oncol 2015; 136:178. http://dx.doi.org/10.1016/j.ygyno.2014.12.022.

48. Sawaya GF, Kulasingam S, Denberg TD, et al. Cervical Cancer Screening in Average-Risk Women: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med 2015; 162:851.

Glossary of Abbreviations:

AIDS – Acquired Immune Deficiency Syndrome

CAC – combined assessment clinic

CDC – Centres for Disease Control

CEDAW - Convention on the Elimination of All Forms of Discrimination Against Women

CEO – Chief executive officer

CIN – cervical intraepithelial neoplasia

CT – computed tomography

DoH – Department of Health

DVI – direct visual inspection

GLOBOCAN – Global Cancer Observatory

GSH – Groote Schuur Hospital

Hb – haemoglobin

HCT – HIV counselling and testing

HIV – Human Immunodeficiency Virus

HOD – head of department

HPV – Human Papilloma Virus

LMIC – low- and middle- income countries

MRI – magnetic resonance imaging

NHLS – National Health Laboratory Service

NP – not positive (inclusive of those patients who were HIV negative and those whose status was not specified)

NS – not specified

Pap Smear – Papanicolaou cervical smear test

PMTCT – prevention of mother-to-child-transmission

SA – South Africa

SSA – Sub-Saharan Africa

Stats SA – Statistics South Africa

STI – sexually transmitted infection

TOP – termination of pregnancy

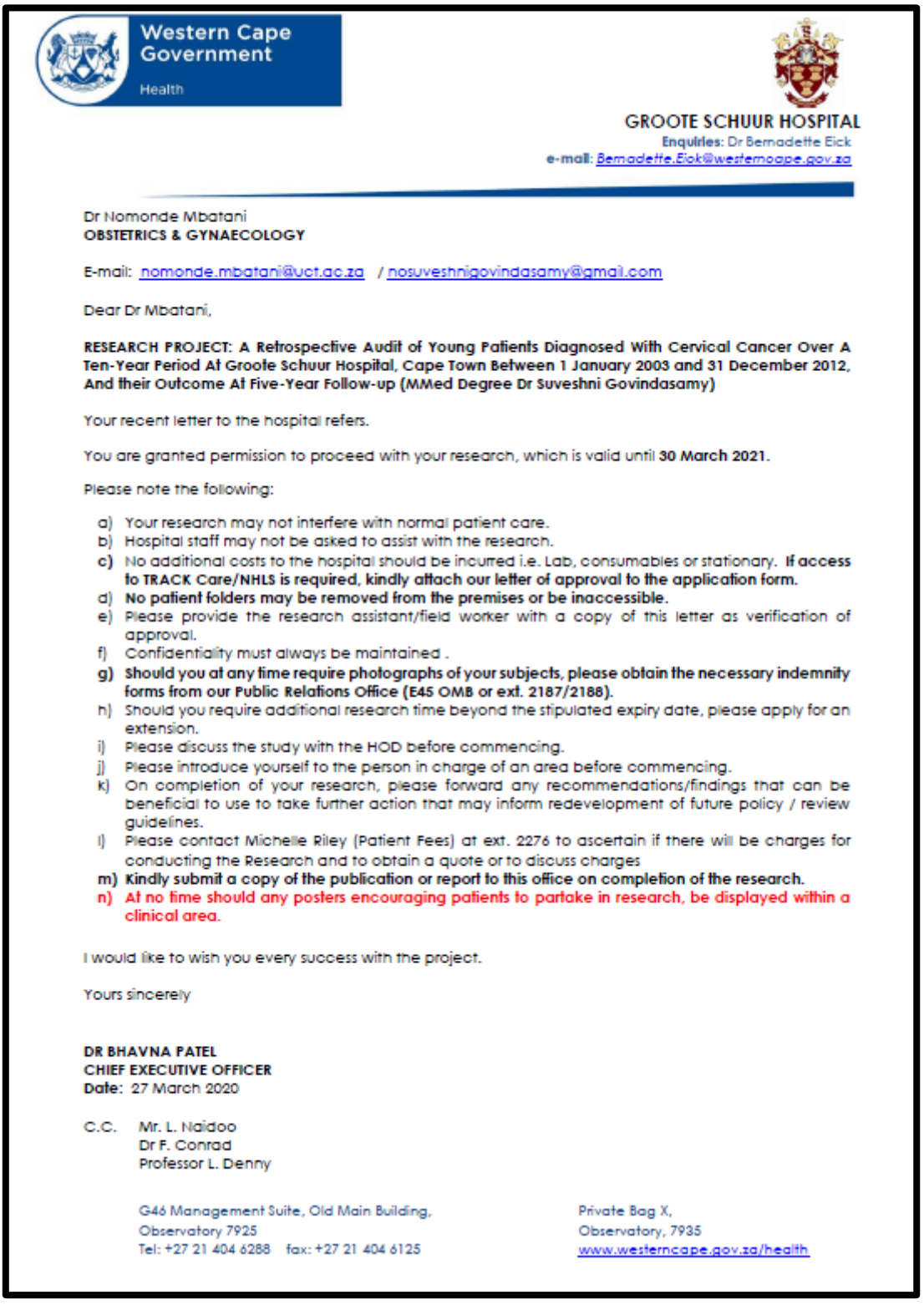
UCT – University of Cape Town

VIA – visual inspection with aceto-acetic acid

VILI – visual inspection with Lugol's Iodine

Appendices

Appendix 1 : *Institutional Consent*



Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bernadette Eick
e-mail: Bernadette.Eick@westerncape.gov.za

Dr Nomonde Mbatani
OBSTETRICS & GYNAECOLOGY

E-mail: nomonde.mbatani@uct.ac.za / nosuveshnigovindasamy@gmail.com

Dear Dr Mbatani,

RESEARCH PROJECT: A Retrospective Audit of Young Patients Diagnosed With Cervical Cancer Over A Ten-Year Period At Groote Schuur Hospital, Cape Town Between 1 January 2003 and 31 December 2012, And their Outcome At Five-Year Follow-up (MMed Degree Dr Suveshni Govindasamy)

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 March 2021.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) No additional costs to the hospital should be incurred i.e. Lab, consumables or stationary. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form.**
d) **No patient folders may be removed from the premises or be inaccessible.**
e) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
f) Confidentiality must always be maintained .
g) **Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).**
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
m) **Kindly submit a copy of the publication or report to this office on completion of the research.**
n) **At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.**

I would like to wish you every success with the project.

Yours sincerely

DR BHAVNA PATEL
CHIEF EXECUTIVE OFFICER
Date: 27 March 2020

C.C. Mr. L. Naidoo
Dr F. Conrad
Professor L. Denny

G46 Management Suite, Old Main Building,
Observatory 7925
Tel: +27 21 404 6288 fax: +27 21 404 6125

Private Bag X,
Observatory, 7935
www.westerncape.gov.za/health

Appendix 2 : *Department Consent from HOD*

Radiation Oncology

Professor Jeannette Parkes
Head of Division

Groote Schuur Hospital, Observatory, 7925, South Africa

Tel: +27 (0) 21 404 4263/5, +27 (0) 21 406 6801 Fax: +27 (0) 21. 404 5259
E-mail: Jeannette.parkes@uct.ac.za

17 March 2020

Dear Dr Suveshni Govindasamy

Permission is hereby granted to Dr Suveshni Govindasamy – Department of Obstetrics and Gynaecology to conduct a research study in the department of Radiation Oncology:

Project title: A retrospective audit of young patients diagnosed with cervical cancer over a ten- year period at Groote Schuur Hospital, Cape Town between 1 January 2003 and 31 December 2012, and their outcome at five-year follow-up

Please note that permission is also required from Dr Eick through Lionel Naidoo's institutional research committee, and from Ethics committee before commencing the research study.

Yours sincerely

Prof Jeannette Parkes
HOD Radiation Oncology Division